THE INTERNAL SECRETIONS

AND THE

PRINCIPLES OF MEDICINE

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TABLE OF CONTENTS OF VOLUME SECOND.

CHAPTER XIII.

PAGE
THE SECRETION OF THE ADRENALS IN METABOLISM 801
The Need of a Secretion to Account for the Respiratory Process. 801
The Adrenal Secretion as the Blood Constituent which Takes up the Oxygen of the Air 805
The Oxidizing Substance (Oxidase) as a Respiratory Constituent of all Organisms 812
The Oxidizing Substance (Oxidase) as the Albuminous Constituent of Hæmoglobin 822
The Red Corpuscles as Storage-cells for the Oxidizing Substance 828
The Adrenal Secretion as the Constituent of Hæmoglobin which, when Oxidized, Produces Bronzing 835
The Active Principle of the Adrenal Secretion as the Active Agent of the Oxidizing Substance 841
Adrenoxidase 850

CHAPTER XIV.

THE ADRENAL ACTIVE PRINCIPLE AS THE FERMENT OF FERMENTS . . 851
Adrenoxidase as a Constituent of Enterokinase and of Trypsin . . 851
Adrenoxidase as "Secretin;" Adrenoxidase Plus Nucleo-proteid as Enterokinase, and the Active Principle of Adrenoxidase as the Ferment of Trypsin 857
The Active Principle of Adrenoxidase as the Ferment of Ptyalin, Amylopsin, Lipase and Maltase, and of the Diastase which Converts Glycogen into Sugar 862
The Active Principle of Adrenoxidase as the Ferment of the Coagulation Ferment, and Rennin as "Fibrinogen Proper." The Zymogen of Fibrinogen Proper . . 869
The Active Principle of Adrenoxidase as the Ferment of Pepsin 875
The Adrenal Active Principle as the Ferment of Ferments; and all Hydrolytic Ferments as Compound Bodies Containing a Zymogen, Nucleo-proteid and Adrenoxidase 878

CHAPTER XV.

THE ADRENAL ACTIVE PRINCIPLE AS THE DYNAMIC ELEMENT OF LIFE AND THE GRANULATIONS OF LEUCOCYTES AS THE LIVING SUBSTANCE 885
The Leucocytes as Tissue Builders 885
The Granulations of Leucocytes as the Granules (Microsomes) of Tissue-cells 896
The Leucocytic Ferments as the Intracellular Ferments of Tissue-cells 907
The Granulations of Leucocytes and Adrenoxidase in the Functions of the Nerve-cell 915
The Granulations of Leucocytes as Living Substance 927
The Active Principle of Adrenoxidase as the Dynamic Element of Life 933
The Active Principle of Adrenoxidase as the Dynamic Element of Life (*continued*) 941

CHAPTER XVI.

PAGE
THE PITUITARY BODY AS GOVERNING CENTER OF VITAL FUNCTIONS. 960
The Pituitary Body as the Governing Center of the Body's Immunizing Functions 960
The Pituitary Body as a Nerve-center........ 966
Nerve-paths from the Pituitary to the Spinal Cord........ 973
The Neural Lobe of the Pituitary as the Seat of the Sympathetic Center 982
The Neural Lobe of the Pituitary as the Seat of Common Sensibility and as the General Motor Center........ 995
The Pituitary Body as the Governing Center of the Adrenals, and as the Thermogenic and Respiratory Center. 1008

CHAPTER XVII.

THE LEUCOCYTES, PITUITARY, THYROID, PARATHYROIDS, AND ADRENALS AS THE FUNDAMENTAL ORGANS IN PATHOGENESIS, IMMUNITY, AND THERAPEUTICS........ 1027
The Leucocytes as the Distributors of Remedies and Poisons... 1027
The Anterior Pituitary as a Lymphoid Organ in which the Products of Leucocytes and any Drug, Poison, or Toxin these Cells may Contain are Exposed to the Test-organ 1037
Leucocytes as the Purveyors of the Thyroid and Parathyroids, and as the Secreting Cells of these Organs........ 1057
The Adrenal System (the Thyroid Apparatus, Anterior Pituitary, and Adrenals Combined) as the Auto-immunizing Mechanism of the Organism........ 1072
The Thyro-parathyroid Secretion as the Sensitizing Substance of all Cells and as the Physiological Excitant of the Test-organ 1087
The Internal Secretions as the Body's Auto-protective Substances and as the Foundation of Rational Therapeutics 1090

CHAPTER XVIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS 1113
The Present Status of Therapeutics........ 1113
The Mechanism of Vasodilation and Its Relations to Organic Function 1115
The Posterior Pituitary the Seat of a Center (the Adreno-thyroid Center) through which the Test-organ Influences the Secretory Activity of the Adrenals and Thyroid Apparatus 1125
Drugs which Enhance the Defensive Properties of the Blood by Promoting the Formation of Auto-antitoxin........ 1134
  Thyroid Preparations 1139
  Mercury 1146
  Iodine and the Iodides 1150
    Iodism 1163
  Adrenal Extractives. (Adrenal Gland, Adrenalin, Epinephrin, Suprarenalin, etc.) 1169
  Antitoxins 1177

CHAPTER XIX.

PAGE

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*) 1185
The Sympathetic Constrictors and the Cranial Stricto-dilators in Organic Function 1185
Drugs which Promote the Formation of Auto-antitoxin and Incite an Artificial Fever by Exciting the Vasomotor and Sympathetic Centers 1201
Idiosyncrasy 1209
Belladonna and Atropine 1210
Drugs which Resemble Belladonna in their Physiological Action 1215
Homatropine Hydrobromide 1215
Hyoscyamus 1215
Hyoscyamine Sulphate 1215
Stramonium 1215
Digitalis 1215
Strophanthus 1222
Drugs which Resemble Strophanthus in their Physiological Action 1225
Apocynum 1225
Convallaria 1225
Sparteine 1225
Strychnine 1225
Drugs which Resemble Strychnine in their Physiological Action 1231
Brucine 1231
Caffeine 1231
Coca and Cocaine 1232
Chronic Cocainism 1237
Quinine 1240
Drugs which Resemble Quinine in their Physiological Action. 1246
Eucalyptus 1246
Drugs which Become Constituents of the Tissue-cells 1246
Iron 1247
Phosphorus 1250

CHAPTER XX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*) 1259
The Sympathetic Center as the Sleep Center 1259
Hypnotism 1265
Excess of Adrenoxidase in Nervous Elements as a Cause of Pain 1267
The Sympathetic Center as the Intermediary Through which Analgesics Produce their Effects 1270
Opium and Morphine 1272
Morphinism 1276
Drugs which Resemble Morphine in their Physiological Action 1281
Codeine 1281
Heroin 1281
Salicylic Acid; the Salicylates 1282
Antipyrin 1282
Acetanilid 1290

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued.*) PAGE

Excitation of the Vasomotor Center and Venosity of the Blood as the Basis of Surgical Anæsthesia 1293
Chloroform 1294
Ether 1299
Nitrous Oxide 1303

CHAPTER XXI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*) 1307
Remedies which Depress the Functions of the Adrenal, Vasomotor and Sympathetic Centers 1307
Arsenic 1310
Chloral 1318
Drugs which Resemble Chloral in their Physiological Action. 1323
Paraldehyde 1323
Sulphonal 1324
Trional 1325
Alcohol 1326
Bromides (Bromides of Potassium, Sodium, Lithium, etc.) .. 1338
Bromism 1339
Veratrum Viride 1342
Aconite 1347
Amyl Nitrite 1350
Nitroglycerin 1354
Drugs which Resemble Nitroglycerin in their Physiological Action 1357
Erythrol Tetranitrate 1357
Creosote, Creosote Carbonate, Guaiacol and Guaiacol Carbonate 1357

CHAPTER XXII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*) 1362
The Blood-plasma of Terrestrial Animals as the Functional Homologue of Sea-water 1362
Marine Salts as Active Participants in the Body's Defensive Functions 1367
Sodium Phosphates 1367
Potassium Phosphates 1367
Alkaline Carbonates 1367
Sodium Chloride 1368
Remedies Used to Influence Special Organs 1373
Purgatives 1374
Castor Oil 1377
Croton Oil 1377
Salines 1377
Mercurials 1377
Emetics 1378
Ipecac 1380
Apomorphine 1380
Diaphoretics 1380
Jaborandi and Pilocarpine 1383
Sweet Spirit of Nitre 1383
Oxytocics (Ergot, Hydrastis, Hydrastinine) 1383

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued.*) PAGE
Drugs which Resemble Ergot in their Physiological Action . 1386
Hydrastis 1386
Diuretics 1387
Saline Solution 1387
Digitalis 1387
Squill 1388
Calomel 1388

CHAPTER XXIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS 1389
The Adrenal System as Immunizing Mechanism, and Cancer . . 1389
Cancer 1390

CHAPTER XXIV.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1426
Convulsive Diseases due to Hypoactivity of the Adrenal System 1426
Tetany 1429
Tetanus 1437
Epilepsy 1454
Epileptoid Disorders 1472
Infantile Eclampsia or Convulsions 1472
Puerperal Eclampsia 1473
Rabies 1486

CHAPTER XXV.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1499
Pain-causing Disorders due to Hypoactivity of the Adrenal System 1499
Gout and Gouty Diathesis 1500
Migraine 1522
Neuritis, Including Neuralgia, Tic Douloureux, Sciatica and Zona (Shingles, Herpes Zoster) 1529

CHAPTER XXVI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1548
Disorders due to Hyperactivity of the Adrenal System 1548
Arteriosclerosis 1548
Angina Pectoris 1565
Cerebral Hæmorrhage 1573
Diabetes Mellitus 1583
Asthenic Glycosuria 1597

CHAPTER XXVII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1608
The Adrenal System in the Infectious Diseases of the Lungs . . . 1608
Pulmonary Tuberculosis 1609

CHAPTER XXVIII.

PAGE
THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1658
The Adrenal System in the Infectious Diseases of the Lungs (*Continued*) 1658
Pneumonia 1659
Broncho-pneumonia 1681

CHAPTER XXIX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1691
The Adrenal System in the Catarrhal and Nervous Disorders of the Respiratory Tract 1691
Acute Bronchitis 1692
Bronchial Asthma 1699
Hyperæsthetic Rhinitis (Hay Fever; Rose Cold, etc.) 1709
Pertussis 1716

CHAPTER XXX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1720
The Adrenal System in the Diseases of the Alimentary Canal.. 1720
Asiatic Cholera 1720
Cholera Morbus 1734
Cholera Infantum 1737
Infantile Diarrhœa 1742
Acute Enteritis 1750
Chronic Enteritis 1753
Typhoid Fever 1758

CHAPTER XXXI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1770
The Adrenal System in the Diseases of the Blood 1770
Anæmia 1771
Pernicious Anæmia 1778
Chlorosis 1784
Hæmophilia 1791

CHAPTER XXXII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*) 1795
The Adrenal System in Infections of the Lymphatic System.... 1795
Syphilis 1795
Plague 1807

INDEX 1815

SUPPLEMENT: Diseases in which one or more glandular products, given alone or with familiar drugs, have given better results than the usual therapeutic measures 1825

ILLUSTRATIONS IN VOLUME SECOND.

PAGE

Leucocyte Granulations in the Act of Penetrating the Cell-body of a Neuron (*Sajous*) 930

The Neuron as an Organ (*Sajous*) 952

Test-organ in Amphioxus in a Young Transparent Individual (after *J. Müller*, slightly modified by *Willey*) 961

Osphradium or Test-organ of a Young Ascidian (drawn after *Van Beneden* and *Julin*) 963

Polynuclear Leucocytes in the Intraparenchymatous Capillaries of the Anterior Pituitary (*Launois*) 1039

The Epithelium of the Anterior Pituitary as Partly Composed of Phagocytic Epithelioid Cells (*Sajous*) 1040

Irregular and Promiscuous Distribution of Cells in the Stroma 1041

Perpendicular Antero-posterior Section of the Pituitary Body of a Human Embryo of Four Months (*Edinger*) 1046

Promiscuous Distribution of Cells in the Anterior Pituitary (*Sajous*) 1046

Section of Anterior Pituitary, Showing Ball-shaped Nerve Terminals Among Cellular Elements (*Berkley*) 1048

Leucocytes which have Shed their Granules, Lymphocytes, etc., in the Act of being Ejected from the Anterior Pituitary (*Sajous*) 1050

Diagram of the Upper Segment of a Sea-squirt, Illustrating the Connection Between the Pituitary Body and the Animal's Respiratory Apparatus (*Parker* and *Haswell*) 1053

Vertical Section Through Thalamus of a Young Alligator, showing the Great-cell (Nucl. magno-cell. strat. gris.) Nucleus of Gray Matter (*Edinger*) 1054

Horizontal Section Through Base of Brain of a Shark, showing Fibers from Great-cell Nucleus (*Edinger*) 1055

Anatomical Relations of the Parathyroids (*MacCallum*) 1067

Section of Dog's Thyroid 150μ Thick, Showing Framework of Follicles, x 180. (*J. Marshall Flint*) 1070

Microphotograph of a Section of the Human Thyroid (*Ferguson*) 1070

Vaso-constrictor Networks Around Arterioles (*Joris*) 1120

Vasomotor Nerves of the Cardiac Coronaries (*Heymans* and *Demoor*) 1186

Effects of Stimulation of the Cervical Sympathetic (*Morat*) 1189

Schema of the Stricto-dilator (Cranial-motor) and Sympathetic Nerves in their Relations to Organic Function (*Sajous*) 1198

Brain-cells of Marmot. Fig. 1, While Awake; Fig. 2, While Asleep (*Querton*) 1264

Fibrosis of Anterior Pituitary Due to Alcoholism (*Sajous*) 1332

Pneumococci and Phagocytosis in Lobar Pneumonia (*Mme. N. Sohultz*) 1670

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CHAPTER XIII.

THE SECRETION OF THE ADRENALS IN METABOLISM.

In the first volume a succinct review of the functions of various ductless glands was submitted, along with the recent corroborative evidence. The following chapters will be devoted mainly to a more detailed study of my views as formulated in 1903 and 1907 and a review of the data which led up to them.

THE NEED OF A SECRETION TO ACCOUNT FOR THE RESPIRATORY PROCESS.

While the blood of vertebrates—fishes, reptiles, birds and mammals—contains both white and red corpuscles, that of invertebrates, with very few exceptions, is not supplied with the latter. Even the blood of Amphioxus, an animal classed among vertebrates, contains no red corpuscles. The presence of hæmoglobin or hæmocyanin in the plasma of various lower forms might be said to afford a means for the absorption and distribution of oxygen; but how are these functions fulfilled?

Again, as stated by Griffiths,[1] "the majority of Invertebrata have white blood, *e.g.*, the Insecta, Crustacea, Mollusca, etc."; and yet, the intracellular processes are hardly more sluggish in many of these than in animals far higher in the phylogenetic scale. This clearly betokens a correspondingly active vital process sustained by active oxygenation. Indeed, there exists in these animals, as well as in the colorless blood of any other organism deprived of red corpuscles or of blood-pigment, a substance endowed with quite as marked an affinity for oxygen as that shown by hæmoglobin in higher forms. What is the nature of this substance?

The process of respiration is ascribed by physiologists to diffusion of gases, and to the affinity of the hæmoglobin in the red corpuscles for oxygen, the red cells absorbing the gas from the plasma as it enters this fluid in order to carry it to all parts of the body. This doctrine fails, however, to explain the respiratory process in the largest division of the animal kingdom, the invertebrates just referred to. The absence of red cells and of their hæmoglobin logically entails, in the present conception of respiration, absence of any agent in the blood having affinity for oxygen; and, unless it can be shown that diffusion alone will satisfy the needs of the process, it is evident that we are left with nothing to account for either the oxygen intake or the carbon dioxide output, or for the manner in which the tissues of these lower organisms carry on respiration.

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[1] Griffiths: "The Physiol. of the Invertebrates," p. 123, 1892.

The weakness of the diffusion doctrine as an explanation of the respiratory process becomes apparent when we take into account the fact, emphasized by Paul Bert[2] many years ago, that an animal will exhaust the oxygen in the air of its lungs even though this be reduced to one-half of one per cent. As stated by Mathias Duval,[3] this shows that "absorption of oxygen by the blood occurs even though the pressure of this gas be almost *nil*." Indeed, Müller observed that when strangulated, an animal exhausted *all* the air in its lungs of oxygen, while Setschenow and Holmgren,[4] Zuntz[5] and others[6] found that "in the last stages of asphyxia the arterial blood contains only traces of oxygen," thus showing that the tissues themselves absorbed this gas through a process of active reduction.

Bohr,[7] using an improved aërotonometer, sustained the conclusions of Robin, Müller, Setschenow and Holmgren and other investigators to the effect that the diffusion doctrine did not satisfy the needs of the respiratory process. He found that the carbonic acid tension was often much lower in the arterial blood than in the alveolar air, and also that the oxygen tension was higher, at times, in the arterial blood than in the latter. He concluded, therefore, that the absorption of oxygen and elimination of carbonic acid were not due merely to diffusion, but to *active* processes where the blood meets the air, *i.e.*, in the pulmonary alveoli. Haldane and Lorrain Smith[8] confirmed Bohr's results. They reached the conclusions that "the *normal* oxygen tension in the arterial blood is *always* higher than in the alveolar air; and is in some animals even much higher than in the inspired air," and that "the absorption of oxygen by the lungs thus cannot be explained by diffusion alone." Moreover, they observed that active absorption of oxygen continued when the oxygen in the alveolar air was artificially increased, the oxygen tension in the blood increasing almost proportionally. This obviously shows that the blood contained some substance which actively reduced the air.

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[2] Paul Bert: C.-r. de l'Acad. des Sci., Oct. 28, 1878.
[3] Mathias Duval: "Cours de physiol.," seventh edition, p. 440, 1892.
[4] Setschenow and Holmgren: Cited by Ludwig: Wiener med. Jahrb., Jahrg. xxi, Bd. i., S. 145, 1865.
[5] Zuntz: Hermann's "Handbuch." Bd. iv, Th. 2, S. 43, 1882.
[6] Pembrey: Schäfer's "T. B. of Physiol.," vol. i, p. 765, 1893.
[7] Bohr: Skandin, Archiv f. Physiol., S. 236, 1891.
[8] Haldane and Lorrain Smith: Jour. of Physiol., vol. xxii, No. 3, p. 231, 1897.

Again, therefore, are we brought to the need of some substance in the lungs capable of absorbing oxygen.

Additional evidence to this effect has been contributed by Vaughan Harley.[9] This observer found that when "one pleural space was filled up so that the lung on one side was compressed, the rate of breathing was increased, and more air was breathed per minute by the active lung than was previously breathed by the two lungs together." This was accompanied "by an increase in the quantity of oxygen absorbed and of carbonic acid eliminated by the animal, the two being increased *pari passu*, so that the respiratory quotient, as a rule, was not altered." After showing experimentally that this could not be ascribed either to an increased rate of respiration alone, to an increase in the temperature, or to displacement of the heart, he concluded that "the only explanation which appears to be satisfactory is that we accept the theory of Bohr."

Bohr's views have met with considerable opposition, though strongly sustained by the comprehensive experiments of Haldane and Smith, Vaughan Harley and older investigators, the antagonism being based on the fact that the gasometric experiments of some observers failed to confirm his results. This objection would have weight did the results recorded by Bohr's opponents agree. But such is not the case; Pembrey,[10] for instance, refers to them as being "very discordant."

This is accounted for, it seems to me, by the fact that gasometric methods do not provide for the absorption of oxygen by other constituents of the blood. That the relative volume of this gas must be decreased while the blood is in transit to the aërotonometer is suggested by Pflüger's[11] observation that arterial blood *used up a portion of its own oxygen* on leaving the animal's vessels. "The blood contains," says Schäfer,[12] "a substance or substances ('reducing substances' of Pflüger) which greedily appropriate any free oxygen which may be present in the plasma, and are even capable of abstracting the oxygen which is combined with hæmoglobin, so that arterial blood rapidly becomes converted into venous blood, when it is not exposed to the access of fresh oxygen. It is not known upon what substance or substances these properties depend." Various factors thus come into play which investigators have not taken into account:—the dimensions of the tube between the animal and the instrument, the friction to which the blood is subjected therein, the time elapsed while it is in transit, etc., all of which are quite sufficient to account for the discordant results obtained. Of course. this applies to Bohr's observations as well, but as with his tonometer "a constant and *rapid* stream of arterial blood could be maintained," while his oxygen ratios exceed those of his opponents, the probability that his results are more exact than theirs is apparent.

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[9] Vaughan Harley: Jour. of Physiol., vol. xxv, No. 1, p. 33, 1899.
[10] Pembrey: Schäfer's "T. B. of Physiol.," vol. I, p. 776, 1898.

In fact, Landois, in his well-known text-book,[13] rejects the diffusion doctrine totally. "The absorption of oxygen from the alveolar air for the purpose of oxidation of the venous blood in the pulmonary capillaries," says this physiologist, "is a chemical process, as the gas-free hæmoglobin in the lungs takes up oxygen to form oxyhæmoglobin. That this absorption depends, not on diffusion of the gases, but on the atomic combination pertaining to the chemical process, is shown by the fact that the blood does not take up more oxygen when the pure gas is respired than when atmospheric air is respired; further, that animals that are made to breathe in a small, closed space will absorb into their blood all of the oxygen but traces, to the point of suffocation. If the respiratory absorption of oxygen were a diffusion-process, much more oxygen would have to be taken up in the first case in accordance with the partial pressure of the gas; while in the latter case such an extensive absorption could not take place."

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[11] Pflüger: Centralbl. f. d. med. Wissen., Bd. v, S. 321, 1867.

[12] Schäfer: *Loc. cit.*, vol. 1, pp. 152 and 153, 1898.

[13] Landois: "T. B. of Physiol.," 10th Amer. Ed., edited by A. P. Brubaker, p. 239, 1905.

Another series of experiments, performed by Bohr and Henriques,[14] further emphasizes the presence in the alveolar walls of a substance capable of absorbing the atmospheric oxygen. Mechanical obstruction of the aorta, if the process had been one of diffusion, should have soon inhibited greatly the respiratory exchanges. These investigators found not only that the exchanges were not as markedly inhibited as is generally believed, but that when, in addition to the aorta, the main branches given off by this vessel were closed, the respiratory exchanges were sometimes *increased*. They reasoned that the absorption of oxygen was due to the presence in the blood of substances "*having greater avidity for oxygen than the blood itself*." That the increased absorption was due to the fact that obstruction of the efferent blood-paths caused the oxyphile substance to accumulate in the lungs, is self-evident.

On the whole, it seems plain that *the respiratory process is carried on through the intermediary of some substance capable of taking up the oxygen of the pulmonary air.* But it is in this connection that Bohr's views have met their only true obstacle. He finally proved the important facts, which several experimenters had previously emphasized, that simple diffusion did not account for the respiratory process and that a powerful reducing secretion was necessary; but he did not reveal the identity of this secretion nor the manner in which it carried on its functions.

This is precisely the function I have found the secretion of the adrenals to fulfill.

THE ADRENAL SECRETION AS THE BLOOD CONSTITUENT WHICH TAKES UP THE OXYGEN OF THE AIR.

Bohr suggested that the pulmonary cells took an active part in the absorption of oxygen and the elimination of carbonic acid gas, basing his hypothesis on the corresponding phenomena observed in the air-bladder of fishes. In 1897, in a paper written in conjunction with Henriques,[15] he deemed it demonstrated that the lungs, "presumably by means of *a kind of internal secretion,*" could "modify the blood's holdings in oxygen and subsequently the distribution of oxygen to the corpuscles and plasma."

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[14] Bohr and Henriques: Arch. de physiol., T. ix, pp. 459 and 819, 1897.
[15] Bohr and Henriques: *Ibid.*, T. ix, p. 819, 1897.

My own conclusion that the secretion of the adrenals fulfilled this all-important function was suggested by the reducing properties of adrenal extractives. Vulpian nearly fifty years ago[16] observed that the expressed juice of the adrenals gave ferric chloride an emerald-green color—the result of the juice's affinity for oxygen, the brownish ferric salt being converted into the green ferrous salt. When suprarenal extracts came into general use they were found to be endowed with the same property. Moore[17] not only found them to be powerful reducing substances, but Cybulski[18] observed that even weak solutions of potassium permanganate destroyed the activity of suprarenal extract, the salt doubtless yielding its oxygen. Battelli,[19] moreover, found that the activity of adrenalin did not become manifest "in the absence of oxygen." Abel, Takamine and other chemists have laid considerable stress on this property, Takamine emphasizing the fact that an aqueous solution of adrenalin becomes oxidized by *contact with the air.*

Inasmuch as the adrenals secrete their product into the blood of the suprarenal veins which open into the inferior vena cava, their secretion must necessarily find its way (*via* the heart) to the lungs. Again, since the blood of the inferior cava meets that of the superior cava in the right auricle, all the blood of the organism, when about to be exposed to the air, cannot but be supplied with a given proportion of adrenal secretion and be evenly distributed by the venous blood among the seven hundred millions of air-cells that the lungs contain.

Proof that the secretion of the adrenals actually passes upward by the inferior cava and that once in the lungs it takes part in the respiratory process, is strikingly furnished by the experiments of Bohr and Henriques,[20] although these observers in no way refer to the adrenals. They found, as we have seen, that when the aorta and the main vessels given off by this great trunk were closed, the respiratory exchanges were often increased—evidence that an accumulation of the oxyphile secretion had occurred in the lungs. Now, matters were reversed when they also closed the only channel through which the secretion passes upward, *i.e.*, the inferior vena cava. "It is only when, along with all other arteries (excepting the coronary arteries)," write these investigators, "the vena cava [above the adrenals as shown by the report of their experiments] was also omitted from the circulation, that the exchanges dropped to the minimum."

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[16] Vulpian: C. r. de l'Acad. des sci. de Paris, Sept. 29, 1856.
[17] Moore: Jour. of Physiol., vol. xvii, p. xiv, 1894-95.
[18] Cybulski: Gazeta Lekarska, Mar. 23, 1895.
[19] Battelli: C. r. de la Soc. de biol., T. liv, p. 1435, 1902.
[20] Bohr and Henriques: *Loc. cit.*

The well-known action of adrenal extractives on the heart affords tangible proof of the passage of this secretion through the cardiac cavities.

The investigations of recent years tend to sustain the view that the heart's power to contract rhythmically is distinctly a property of the cardiac muscle. Small pieces of the ganglion-free apex of the frog's heart, strips of the ventricle of the tortoise, etc., will beat rhythmically a long time when placed in suitable media, blood serum or artifically prepared fluids, saline solution, etc., especially if these contain calcium and potassium salts, and if they are kept supplied with oxygen under pressure. Yet "it must also be borne in mind," writes Stewart,[21] "that when we have localized the essential mechanism of the rhythmical contraction in the muscle of the heart, we have still to ask whether this mechanism is not put into action by some stimulus external to the muscle." My investigations have led me to ascribe this function to the secretion of the adrenals.

As far back as 1853, Brown-Séquard[22] emphasized the importance of the venous blood in cardiac dynamism. While admitting that arterial blood tended to promote the contractile power of the cardiac muscle, he contended that the contractions were due to a stimulating action of the venous blood. The erroneous belief that CO_2 was the energizing agent soon caused this view to be antagonized successfully. When the CO_2 is left out of the question, however, it becomes evident that the blood of the inferior vena cava *does* contain a principle capable of contracting the heart-muscle. Oliver and Schäfer[23] and others have demonstrated conclusively that intravenous injections of adrenal extract produce "a powerful physiological action upon the muscular system in general, but especially upon the muscular walls of the blood-vessels, and the muscular wall of the heart." My own researches on the ox heart[24] have led me to conclude that some of the adrenal secretion which enters the heart with the blood of the inferior vena cava—which contains of course only *reduced* oxyhæmoglobin—penetrates into the myocardium by way of the Thebesian foramina and that it plays a leading part in cardiac contraction. Mousset[25] also contends that the adrenal secretion acts directly on the heart muscle. As the adrenal secretion inevitably enters the heart with the blood of the inferior vena cava, it is difficult to conceive how it can fail to influence cardiac dynamism.

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[21] Stewart: "Manual of Physiology," fourth edition, p. 131, 1900.

[22] Brown-Séquard: "Experimental Researches applied to Physiology and Pathology," p. 104, 1853.

This accounts not only for the experimental results recorded by Brown-Séquard, but also for the now well-known powerful action of adrenal extractives in the various forms of cardiac adynamia shown by Reichert,[26] Crile,[27] Martin and Pennington,[28] and others. Moreover, Beaman Douglass[29] found that when the ventricles of a turtle's heart were detached from its auricles and left in the open air, they began to beat at once when immersed in a 0.001 suprarenal solution. This shows that its action on the heart is independent of the nervous supply of this organ, a fact also suggested by the increase in force of the contractions which occurs, as emphasized by Wallace and Mogk,[30] when "the vagus influence is removed."

That the adrenals supply to the blood of the inferior vena cava a substance capable of provoking the phenomena obtained by *intravenous* injections of adrenal extractives is also fully sustained experimentally. Considerable evidence to this effect has already been submitted in the first volume. A summary of this evidence, enriched by facts found in literature since, may prove helpful at this stage.

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[23] Oliver and Schäfer: Jour. of Physiol., vol. xvi, p. 1, 1894; and vol. xvii, p. ix, 1895.

[24] Cf. vol. i, pp. 421-454 of the first three editions.

[25] Mousset: "Les principes actifs des cap. surrénales," 1903.

[26] Reichert: Univ. of Penna. Med. Bull., Apr., 1901.

[27] Crile: Boston Med. & Surg. Jour., Mar. 5, 1913.

[28] Martin and Pennington: Amer. Med., Nov. 21, 1903.

[29] Beaman Douglass: Amer. Jour. Med. Sci., Jan., 1905.

[30] Wallace and Mogk: Amer. Jour. of Physiol., vol. ii, p. v, 1899.

Gottschau[31] observed in histological preparations of the adrenals that protoplasmic masses projected from the medullary cells into the central vein of the organ, and that very slight pressure upon the latter would cause blood containing these masses to issue from it. They then assumed the aspect of bright, intensely refractive and colorless granules, which, singly or in clumps of fifteen or twenty, were contained in the blood issuing from the organ. Manasse[32] also noticed that hyaline masses were secreted by rows of cells in the medullary canal of the adrenals and that they then passed into the vessels of the latter. A similar observation was recorded by Auld,[33] who refers to the secretion as a colloid. Stilling[34] found the granules referred to by Gottschau not only in the cortical and medullary layers, but also in the tissue spaces. Pfaundler[35] discovered similar granules in the lumina of the adrenal vessels and in the *suprarenal* vein where it opens into the vena cava.

Again, Cybulski and Szymonowicz[36] having convinced themselves of the correctness of Brown-Séquard's conclusion that in animals from which both adrenals had been removed, the ensuing symptoms could all be arrested by intravenous injections of extracts of the glands, ascertained experimentally that living adrenals secreted the substance which gave adrenal extracts their characteristic properties, and that blood drawn from the suprarenal veins produced effects similar to those that follow injections of these extracts. Langlois[37] was able to corroborate these results. They were also confirmed by Dreyer in a series of experiments referred to below. Biedl[38] ascertained that while fresh blood from *other* veins produced practically no effect when slowly injected intravenously, blood taken from the adrenal veins injected in the same way caused the characteristic pulse and blood-pressure curves, *i.e.*, a primary slight rise due to the addition of the fluid, followed a few seconds later by an increase of volume and slowing of the pulse, and from one to one and one-half minutes later by the maximum rise of blood-pressure.

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[31] Gottschau: Archiv f. Anat. u. Physiol., Anat. Abth., S. 412, 1883.

[32] Manasse: Archiv f. path. Anat., Bd. cxxxv, S. 263, 1894.

[33] Auld: Brit. Med. Jour., May 12, 1894.

[34] Stilling: Arch. f. Path. Anat., Bd. clx, S. 234, 1887.

[35] Pfaundler: Sitzungs-Bericht d. k. Akad. d. Wissensch. mathem. Bd. ci, S. 3, 1892.

[36] Cybulski and Szymonowicz: Gazeta Lekarska., Mar. 25, 1895.

[37] *Langlois*: Revue scientifique, p. 303, 1897.

[38] Biedl: Archiv f. d. gesam. Physiol., Bd. lxvii, H. 9 u. 10, S. 443, 1897.

All this is further emphasized by experimental stimulation of the nerves supplied to the organs. To ascertain, if possible, the identity of their secretory nerves, Biedl tied the vena cava above and below the adrenal veins and inserted a cannula into the vena cava, suspending the nozzle of the instrument over a small drum connected with a recorder. The number of blood-drops falling upon the drum in a given time, as the blood-pressure in the vessels was increased by stimulating the nerves distributed to the adrenals, could thus be accurately recorded. Having cut both splanchnics in the thoracic cavity, he stimulated the peripheral ends electrically. "During the first 6 to 9 seconds," says the physiologist, "the number of drops remained the same; at the 7th second—sometimes later, about the 10th—a gradual increase in the number of drops occurred, until 20 to 25 seconds had elapsed, when the number of drops multiplied 3 to 5 times." The increased flow continued from 10 to 20 seconds *after* the current was no longer applied, and also after the increased pressure in the organ's vascular supply, caused by the current, had ceased. The effects could no longer be obtained when the suprarenal nerves, which are remarkable for their size, were severed. Although Biedl was thus able to demonstrate that the splanchnic contained fibers which, when stimulated, increased the flow of blood through the adrenals, he did not succeed in establishing their identity as secretory nerves.

To settle this important feature of the problem, Dreyer,[39] in a series of experiments, placed a ligature around the vein on either side of the gland, the ligature "on the mesial side serving to tie off the central end of the vein, the other, on the lateral side, being used to tie in the cannula," a straight glass tube. In this way, the blood from the tube issued with certainty from the gland. Specimens of the blood were then collected from the femoral vein, from the adrenal vein before stimulation, and from the adrenal vein during stimulation. The comparative effects of these various bloods when injected intravenously into the animals from which they had been obtained or into others, were then carefully recorded. The eight experiments reported demonstrated that excitation of the cut splanchnic not only increased the blood-flow, but also the proportion of secretion in that blood. Both sets of animals—those from which the blood had been taken and the controls—when "stimulation" blood was injected into them, showed a corresponding increase of the characteristic effects of adrenal extract. Briefly, using Dreyer's words: "A given bulk of adrenal blood taken during stimulation [of the cut splanchnic] had a decidedly greater effect than the same bulk of normal blood, meaning by normal blood that which was taken when not stimulating." The present status of the question was reviewed in the first volume.

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[39] Dreyer: Amer. Jour. of Physiol., vol. ii, p. 203, 1899.

It is plain, therefore, that the secretion of the adrenals themselves produces effects similar to those caused by intravenous injections of adrenal extracts. That this applies to human adrenals was found by Guinard and Martin, who used the expressed juice of adrenals derived from an executed criminal.

Finally, the symptoms of certain diseases or that follow extirpation of the adrenals strikingly emphasize a connection between these organs on the one hand and the heart and respiratory process on the other. In Addison's disease, for example, the *systole* is greatly weakened and the pulse is small, extremely soft and compressible. Lowering of general metabolism—due to lowered general oxygenation—is shown by the facts that the temperature, when no complication is present, is subnormal, and that the extremities are cold. Rolleston in Allbutt's Practice[40] states that a cadaveric odor is sometimes emitted by these cases—a self-evident sign of lowered vitality. As emphasized by Sergent and L. Bernard,[41] the identical symptoms ascribed to Addison's disease are met with in the many distinctive disorders of which the adrenals may be the seat.

The effects of removal of these organs have been reviewed at length in the first volume. Most prominent among these, however, are, as first shown by Brown-Séquard, lowering of the temperature and of the blood-pressure, accompanied by intense weakness, hardly perceptible heart-beat, very weak and rapid pulse, etc. That we are dealing with morbid phenomena due to absence of the *secretion* of these glands was also demonstrated by Brown-Séquard, extracts prepared from healthy adrenals and administered subcutaneously having restored the experimental animals as long as the extracts were used.

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[40] Rolleston: Allbutt's "Practice," vol v, p 540, 1897.
[41] Sergent and L. Bernard. Arch gén. de méd., July, p. 27, 1899.

Pathological and physiological evidence, plus new data submitted in the first volume, (1920) thus unite in pointing to the secretion of the adrenals as the *constituent of the blood which absorbs the oxygen of the air, in order to carry on oxygenation of the body at large.* We have seen that this has been confirmed.

THE OXIDIZING SUBSTANCE (OXIDASE) AS A RESPIRATORY CONSTITUENT OF ALL ORGANISMS.

In the first volume, I showed that the secretion of the adrenals lost its identity as such when it reached the lungs, and that when the venous blood had been exposed to the air of the alveoli and had become arterial, it contained a new substance, the oxidizing substance. This compound was then traced with the plasma into the minute capillaries of the cellular elements of the various organs and into the axis-cylinders of the nerves, neuro-fibrils, etc., and shown capable, moreover, of subserving therein not only the needs of nutrition, but also those of active function—in so far, at least, as the oxygen can contribute to these processes.

Exception has been taken to my conclusions on this score on the plea that the blood-plasma *per se* did not contain such a substance, this being based on results obtained with the gas-pump. We have seen, however, that shed blood does not give even an approximate idea of the oxygen-content of living blood, its oxygen being rapidly reduced by another constituent. This applies to defibrinated blood as well, since the fibrin itself carries off a large proportion of the oxygen. The gas-pump is as useless an instrument in this connection as the aërotonometers referred to in the preceding section, and like them has contributed much to prevailing misconceptions.

The blood-plasma of animals, including man, not only contains such an oxidizing substance, but its presence may be demonstrated at every stage of organic life, *i.e.*, in the vegetable and animal kingdoms. So important is this feature of the problem, in fact, that I deem it necessary to review some, at least, of the evidence at our disposal to this effect.

Stress was laid in the earlier editions of this work on the presence in the blood of what Schmiedeberg (1876 and 1881), Salkowski, Jaquet, and Abelous and Biarnès had characterized as an "oxidizing ferment," freely soluble, as shown by Jaquet, in the blood fluids. Claude Bernard, Pavy and Lépine had found that the plasma could oxidize sugar, the process being accompanied by the production of carbon dioxide, according to Kraus. This was also found by Pohl, Spitzer and other observers to apply to intracellular or tissue juices. Importance was attached to the fact that Abelous and Biarnès had, in 1895, "succeeded in causing oxidation of salicylic aldehyde by means of blood-serum, that is to say, *blood absolutely deprived of its corpuscles*," and furthermore, that these chemists had found, as had Salkowski and Jaquet, that the passage of air through the blood during the experiment was an essential factor of the oxidation process. These experiments thus made it evident that the oxidizing ferment in the blood-serum could *absorb the oxygen of the air and then transfer it* to the salicylic aldehyde, converting the latter into salicylic acid. The importance of this fact, with respect to the general question in point, is very great, since it shows that the oxidizing ferment referred to can fulfill precisely the rôle generally ascribed to the *corpuscular hæmoglobin*. In other words, while it is believed that this hæmoglobin carries the oxygen from the seat of external respiration, the pulmonary alveoli, to the seat of internal respiration, the tissue-cells, the foregoing experiments have shown that the *plasma* contains "oxidizing ferments" or "oxidases" capable of carrying on this identical function.

Now, it happens that physiologists have failed so far to discover the identity of an important constituent of hæmoglobin. Gamgee,[42] for instance, after reviewing our knowledge of hæmoglobin, concludes that "without attempting to speculate beyond the facts which we possess"........"it may be assumed that hæmoglobin exists in the blood-corpuscles in the form of a compound with a yet *unknown constituent* of the corpuscle."

It happens also that the blood contains a group of oxidizing ferments, or oxidases, the origin or source of which, in animals, has *not been found.* That these are also prominent factors of the vital processes is suggested by Howell's[43] concluding remark, after reviewing briefly the most salient available data, that "such facts as these lend great probability to the belief that eventually it will be shown that the oxidations in the body are effected by the influence of oxidases or peroxidases acting singly or in combination or in sequence with the hydrolytic enzymes."

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[42] Gamgee: Schäfer's "T. B. of Physiol.," vol. I, p. 189, 1898.

Again, Moritz Traube,[44] in 1858, called attention to the need of some substance in the blood which could act as intermediary between hæmoglobin and tissue-cells to account for various phenomena witnessed. The term "oxidase" was introduced to describe ferment-like bodies which, without themselves undergoing destruction, could so influence oxygen as to increase greatly its oxidizing activity. In 1858, Traube[45] had already emphasized the need of such a substance to explain the physiological action of the oxygen carried to the tissues by the hæmoglobin—a substance which, he thought, could take up oxygen from the oxyhæmoglobin and transfer it to the tissues, thus acting as an "oxygen transmitter." Experimental demonstration of the existence of a body endowed with such properties was not made, however, until 1876, when Schmiedeberg[46] published his first paper. His investigations, and particularly those of Jaquet and the other chemists referred to above, having shown that the blood-*serum* contained a substance which could absorb oxygen from the air and then surrender it to reducing substances, the requirements of cellular metabolism outlined by Traube were met. It could act, in keeping with the latter observer's conception, as an "oxygen transmitter."

That a ferment was the active factor of the process was demonstrated a few years later. In 1883 a Japanese chemist, Hikorokuro Yoshida,[47] found that the lacquer-forming juice of *Rhus vernicifera* underwent, while hardening, slow oxidation. He ascribed this phenomenon to a diastase which lost its power as such when heated to the boiling point. A French chemist, however, G. Bertrand,[48] succeeded in isolating the ferment itself and termed it "laccase." The juice from which he isolated this body was obtained by incising the tree *Rhus succedenea.* He found that this cream-like juice could be kept in its normal state a long time in well-stoppered bottles, but that as soon as it was *exposed to the air*, it became *brownish*, and soon acquired a thin, intensely black layer, insoluble in ordinary solvents and resisting the action of liquid alkalies and acids, *i.e.*, lacquer. The process was due, as stated by Bertrand, to the very active absorption of oxygen from the air by the laccase and oxidation of the remaining bodies of the juice, collectively known as "laccol." It is plain that in order to do so, laccase acted as "oxygen transmitter."

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[43] Howell: "Text-book of Physiol.," p. 836, 1905.
[44] Traube: "Theorie der Fermentwirkungen," Berlin, 1858.
[45] Traube: *Loc. cit.*
[46] Schmiedeberg: Archiv f. exper. Path. u. Pharm., Bd. vi, S. 233, 1876.
[47] Hikorokuro Yoshida: Jour. of the Chemical Soc., vol. xliii, p. 472.

This latter process, and the fact that oxidation actually occurred, Bertrand was able to prove experimentally. Thus, 1 gramme of hydroquinone in a one per cent. solution, shaken three hours in the presence of but 0.1 gramme of laccase and 174.9 cubic centimeters of air was found to have *absorbed* 25.4 cubic centimeters of oxygen. Even more (32 cubic centimeters) was taken up in a second experiment, in the presence of more air. In another investigation the *carbonic acid output* was also ascertained, the ratios being 23.3 cubic centimeters of O absorbed to 13.7 cubic centimeters of CO_2 output in one experiment, and 20.8 of O absorbed to 16.4 of CO_2 in the second. A large number of plants of various kinds were then analyzed by Bertrand[49] and found to contain this laccase. With Bourquelot,[50] he also found it in mushrooms, in gum arabic, etc. It is through the intermediary of laccase that, for instance, pyrogallol, gallic acid, tannic acid and other familiar substances are oxidized.

A property among others which distinguishes any vegetable or animal fluid or tissue that contains the "oxygen transmitter" is that of causing tincture of guaiac to become blue. This phenomenon was first observed in the nineteenth century by Taddey, Rudolphi, and Planche, the latter observer having found that boiling of an organic substance caused its fluids to lose this property; but it was only when Schoenbein, the discoverer of ozone, took up the question in 1856[51] and showed that many plants gave the guaiac blue test, that it began to receive serious attention. Since then, oxidases have been found by various investigators in so many plants that their presence may be regarded as universal. Indeed, referring to an oxidase he named "catalase"—a term which implies the function of "oxygen-transmitter" *i.e.*, *catalysis*—Oscar Loew[52] wrote after a very large number of experiments: "There does not exist a group of organisms or any organ or even a single vegetable or animal cell that does not contain some catalase, as far as the observations of the writer go. This general occurrence of catalase in the organized world cannot be accidental and must have a certain significance." The oxidizing property was combined with that of catalysis (oxygen-transmission) in all these organisms precisely as in the case of the plants studied by Bertrand—and also in that of animals, as we shall see presently.

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[48] G. Bertrand: Archives de physiol., T. viii, p. 23, 1896.
[49] Bertrand: C. r. de l'Acad. des sci., T. cxxi, p. 166, 1895.
[50] Bourquelot: C. r. de la Soc. de biol, 2e Série, T. II, p. 579, 1895.

One still meets occasionally in literature with the statement that respiration in plants is the opposite of that in animals, *i.e.*, that while the latter take up oxygen from the air, plants absorb carbonic acid. Sachs showed over thirty years ago, however, that such is not the case. The absorption of carbon dioxide and excretion of oxygen by the chlorophyll of the leaves is concerned with the nutrition of the plant only; and this occurs in the daylight, while respiration goes on both day and night. The plant takes up oxygen from the surrounding air and gives off carbon dioxide, precisely as do animals. This fact adds greatly to the interest of the experimental data just outlined. Indeed, so strikingly like the respiratory process were the gasometric results obtained by Bertrand that, although his experiments aimed only to establish the identity of the ferment which caused the oxidation of lacquer, he refers to them as being "the first example of diastatic reaction with interchange of gases." He also says that "it is all the more remarkable in that it [the interchange] resembles in a way artificial respiration, and one may at least suppose that it represents a phenomenon very nearly akin to that attending respiration in the vegetable kingdom." As interpreted from my standpoint, this does not exemplify *artificial* respiration, but instead, the foundation of the true respiratory process of plant-life.

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[51] Schoenbein: Cited by P. Sée: Arch. gén. de méd., July 14, 1906.
[52] Oscar Loew: "Catalase," U. S. Dept. of Agriculture Rep., No. 68, 1901.

The blood of many invertebrates, which contains no blood-pigment, hæmocyanin or hæmoglobin, has likewise been found to contain an oxidase, or oxidizing ferment.

Piéri and Portier[53] studied experimentally the blood of mollusks to ascertain whether it contained an oxidizing ferment. Freshly prepared tincture of guaiac had been found by Bertrand to turn blue when in contact with his laccase. The labial palps of acephalic mollusks when dipped in a few drops of water to which one or two drops of tincture of guaiac had been added, showed blue streaks; the water also soon became blue. A similar effect was produced when the juices of a palp were dropped in the same solution. That this was not due merely to oxygen liberated by the living cells is shown by the fact that when Piéri and Bertrand exposed both the palp and the liquid to a temperature of 50° to 60° C., the activity of the oxidizing substance was enhanced. Now, Salkowski[54] has shown that the oxidizing body in the plasma is only destroyed at 100° C. (212° F.), the boiling point, thus identifying it as a ferment. Important in this connection is the fact, previously referred to (page 804), that when the blood leaves the arteries, its oxygen is rapidly exhausted by a plasmatic constituent. This is the substance, as will be shown later, that is destroyed between 50° and 60° C. The conclusion of Piéri and Portier that the effects witnessed were ascribable to an *oxidizing* ferment is thus clearly sustained. The gills, treated in the same way, gave identical results; so did an emulsion of thirty-six macerated sets of gills and palps—a saturated solution of salicylic acid being used in its preparation to eliminate all possibility of bacterial intervention.

These results, as emphasized by Piéri and Portier, could not be ascribed to corpuscular, *i.e.*, iron-containing hæmoglobin. A solution of this pigment, whether prepared with distilled water or with a saturated solution of salicylic acid, turned muddy-red when tincture of guaiac was added thereto.

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[53] Piéri and Portier: Archives de physiol., T. ix, p. 60, 1897.
[54] Salkowski: Archiv f. path. Anat., Bd. cxlvii, S. 1, 1897.

Heated to the boiling point a few minutes, a solution (whether prepared with salicylic acid or not) of macerated tissues such as the above no longer gave the guaiac reaction, notwithstanding prolonged shaking in the presence of air. Heated to 90° C., however, a portion of this solution gave a precipitate which, after being rapidly dried on blotting paper and dissolved in distilled water, gave the reaction. A similar precipitate allowed to dry in the laboratory air first became gray, then *black.* Placed in water in this condition, it did not dissolve, and the liquid did not give the guaiac reaction, thus showing that it had been oxidized by taking up the *oxygen of the air.* Precisely the same results had been obtained by Bertrand with laccase.

The gills and palps of mollusks were found particularly active as compared to the blood. As these organs had given a positive reaction with other reagents, guaiacol in concentrated solution in distilled water (Bourquelot[55]) was used as control. This agent gives an orange-red color to a solution containing the oxidizing ferment. The gills of sixteen *Ostrea edulis* (oyster) were left three days in a saturated solution (90 cubic centimeters) of salicylic acid, then filtered. Three cubic centimeters of this extract were then added to a guaiacol solution, and an equal quantity to distilled water. The first solution became red; the second remained clear. These tests were controlled, in turn, by means of two others, the hydroquinone and pyrogallol tests, with positive results. Hashed gills proved as active. Positive results were also obtained with blood (excepting when boiled) from other parts of the body, but Piéri and Portier specify that the *gills* and *palps* respond most actively to the reagents. I have repeated some of these experiments in the clam, oyster and sea mussel, and obtained identical results. The similarity between the chemical properties peculiar to the blood of the respiratory organs of mollusks, the oxidizing ferment and the vegetable ferment laccase, is evident.

Crustaceans were found by Abelous and Biarnès[56] to correspond with mollusks as to the presence of an oxidizing ferment. The hæmolymph of crayfish gave a positive reaction not only with the tincture of guaiac, but also with other reagents used. Heating to 60° C. did not prevent the reaction, but the latter no longer occurred after the boiling point had been reached. With Rohmann and Spitzer's reagent (a solution of paraphenylene-diamine), which gives a solution containing the ferment a violet color, Abelous and Biarnès obtained but a very slight reaction with generative organs and muscles, and *decoloration* of the reagent in the case of the liver—due to reduction—followed by intense violet coloration. Both actions of the ferment, reduction and oxidation, were thus manifest. The *gills* showed a marked reaction, and the violet color persisted.

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[55] Bourquelot: C. r. de la Soc. de biol., Nov. 7, 1896.
[56] Abelous and Biarnès: Archives de physiol., T. ix, p. 277, 1897.

In a second set of experiments, the liver again showed the two phases of action, while other organs responded only slightly or not at all to the guaiac test, but the *gills* became blue "*very rapidly* and *energetically.*" The guaiacol, hydroquinone and pyrogallol tests also gave positive results. A precipitate obtained with alcohol, when dried and dissolved in distilled water, gave similar results, thus showing that the investigators were dealing with the typical oxidizing ferment. An important feature of these experiments is that when an extract of gills, a solution of pyrogallol, and water were placed in a tightly closed flask containing air, Abelous and Biarnès ascertained gasometrically not only that oxygen had been consumed, but that *carbonic acid had been evolved.*

The respiratory organs of these crustaceans clearly showed, therefore, that they contained the specific ferment. It became evident, also, that the function of these organs was to absorb oxygen and to transmit it to the elements represented by the pyrogallol in the reaction, namely, the tissue-cells.

That a close connection between the oxidizing ferment and the respiratory process actually exists is emphasized by experiments in vertebrates. In those of Schmiedeberg, Jaquet, Salkowski, Abelous and Biarnès, the tissues of higher mammals, the horse, ox, calf, etc., were used; a fact which suggests that the domain of the oxidizing ferment is limitless in organic life. In batrachians, whose adrenals consist of a narrow patch along each kidney and are connected with the main blood-vessels, arterial and venous, as in man, a direct connection between the oxidizing ferment and "the respiratory function" has been sug-

61354

gested by C. Phisalix[57] (though this author, of course, refers in no way to the adrenals in this connection), as Bertrand had in respect to plants.

Phisalix justly contended that if oxidizing ferments actually presided over the chemical phenomena of respiration, they should be present in tissues, such as the skin, that are capable of carrying on supplementary respiratory functions. He therefore studied the subject in *Rana esculenta* and *temporaria* and *Bufo vulgaris*. The skin of these batrachians was allowed to macerate in salt water and the solution thus obtained was placed in three tubes: the first specimen was boiled; the air in the second was removed and the tube sealed; the third was left open, and its solution exposed to the air. The contents of the first two tubes remained unchanged; that of the third became brown, the color proceeding downward from the surface. After a few days the liquid had become almost black. The connection between these and Bertrand's experiments in plants is obvious. Now, we have seen that boiling destroys the ferment, thus accounting for the first tube's unchanged state; sealing of the second deprived it of air, thus showing that *oxygen* was indispensable to the assumption of the *brown color*. Phisalix further proved the presence of the oxidizing ferment in the batrachian blood by submitting the expressed juice of frog's skins to the guaiac test. The blue color appeared here as it had in plants and invertebrates, thus showing that the ferment could not only absorb oxygen, but also surrender it to reducing agents. The skin typified the lung surface, *i.e.*, the *external* respiration, in these experiments, and the guaiac the tissue elements, *i.e.*, the *internal* respiration.

Additional evidence to the effect that the blood contains an oxidizing substance is that a similar substance is present in the liquid portion of milk, which, as stated in the first volume, corresponds with and is derived from the blood-plasma.

The first to draw attention to these reactions was Arnold,[58] who showed that "fresh cow's milk on the addition of a little tincture of guaiac, gives a *blue* color of varying intensity." He ascribed this phenomenon to the presence of ozone, but subsequent labors showed its true identity. Dupouy,[59] Raudnitz,[60] Gillet,[61] Nobécourt and Merklen,[62] and others have also found oxidase similar to that in blood. Spolverini[63] observed that it possessed glycolytic properties identical to those of oxidase.

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[57] C. Phisalix: Jour. of physiol., vol. xxiii, Suppl., p. 49, 1899.
[58] Arnold: Arch. d. Pharmak., Nu. 41, 1881.

As we will see farther on, Abelous and Aloy[64] recently found that the *catalytic* action of the oxidizing substance was most active in the absence of air—precisely the condition that prevails in tissue respiration, *i.e.*, cellular metabolism.

Bourquelot[65] showed in 1897 that while milk could not itself oxidize directly, it could act as reducing agent and then oxidize. This action proved to be due to a substance to which he applied the term "anaeroxydase"—*i.e.*, a ferment capable of carrying on the oxidizing process in the absence of air, by means of oxygen derived from other constituents of the medium of which it is itself an occupant.

Returning to the blood of higher animals, we must not lose sight of the fact that all tests indicating the actual presence of an oxidizing substance were based on the action of tissues upon reducing substances. As this might be ascribed to an excess of oxygen in these tissues irrespective of the presence in the blood-stream of any oxidizing agent, it is necessary to show that the blood itself can respond actively to guaiac. We have but to recall that the guaiac test is, in medical jurisprudence, one of the most reliable in the detection of *human* blood-stains, even in the absence of hæmatin, the iron-containing constituent of hæmoglobin. Seifert[66] not only found that an almost colorless solution became "either at once or in the course of a minute or two, intensely blue," but that the test "frequently demonstrates the presence of blood when the result of the spectroscopic test is negative and hæmatin crystals cannot be obtained."

Finally, Jolles[67] demonstrated more recently that the human blood contained both oxidase and catalase (one and the same body, we have seen) and that the catalasic, *i.e.*, catalytic, power of the blood appeared to have a definite relation to the number of red corpuscles. This suggests clearly a relationship between these bodies and respiration; indeed, Duclaux[68] has expressed the belief that "oxydases are the diastases of respiration."

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[59] Dupouy: Thèse de Bordeaux, 1897.
[60] Raudnitz: Centralbl. f. Physiol., Bd. xii, S. 790, 1898.
[61] Gillet: Jour. de phys. et de path. gén., T. iv, p. 439, 1902.
[62] Nobécourt and Merklen: La presse méd., Dec. 24, 1902.
[63] Spolverini: Atti del iv, Congr. Ital. de Pediat., 1901.
[64] Abelous and Aloy: C. r. de la Soc. de biol., T. lv, p. 891, 1903.
[65] Bourquelot: Jour. de pharm. et de chimie, T. v, 1897.
[66] Seifert: Vierteljahresschrift f. gerichtl. Med., Bd. xvi, H. 1, S. 1, 1898.
[67] Jolles: Münch. med. Woch., Nov. 22, 1904.

On the whole, this evidence has been submitted to show (1) *that an oxidizing substance occurs in the blood of all living organisms, i.e., from plant to man;* (2) *that it is a respiratory function that it subserves in both kingdoms, not only in so far as the tissues themselves are concerned, but also in respect to the organs which serve for the absorption of oxygen from the surrounding media: the gills, skin, and lungs;* (3) *that in all organic life, plants, invertebrates and vertebrates, this oxidizing substance absorbs oxygen, and liberates it, thus acting as an "oxygen transmitter," i.e., as a catalyser.*

What is the relationship between this oxidizing substance or oxidase and hæmoglobin?

THE OXIDIZING SUBSTANCE (OXIDASE) AS THE ALBUMINOUS CONSTITUENT OF HÆMOGLOBIN.

Hæmoglobin, as we have seen, occurs only in the blood of animals already far advanced in the evolutional scale, to increase, according to zoölogists, its capacity for oxygen. As red corpuscles appear in still higher organisms, *i.e.*, only in vertebrates—a relatively small proportion of the animal kingdom—it seems evident that they, too, are tardy additions intended still further to increase the blood-plasma's efficiency as an oxygen carrier *pari passu* with the increasing needs of the higher animals. This is a necessary feature of their development, since, as shown by Claude Bernard, Magnus, Lothar Meyer, and Hoppe-Seyler, the blood "holds in solution an amount of oxygen greatly in excess of that which could exist in a state of simple solution." The history of the red corpuscle thus suggests that it acts as a storage-cell for the oxidizing substance, oxidase or catalase, which, in the light of the foregoing evidence, is required to account for tissue respiration.

With which of the known constituents of the blood-plasma or of corpuscles do these oxidizing bodies correspond?

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[68] Duclaux: *Loc. cit.*

The identity of this substance suggests itself when a source of confusion is eliminated, *viz.*, the prevailing belief that tissue metabolism is accomplished by, or is due to, oxidation of tissue elements, and that the tissues are the seat of an exchange of oxygen and carbon dioxide similar to that believed to prevail in the lung.

C. R. Barnes, professor of plant physiology at the University of Chicago, wrote recently:[69] "I diligently examined the most modern and most thorough text-books on physiology," naming several familiar to us all, "but in them I found no treatment whatever, indeed no mention whatever, of the real problems of respiration, that is, of what is happening in the tissues, the processes of which these external phenomena are the sign........The respiratory ratio has proved a veritable will-o'-the wisp, leading investigators into a bog where their labors and their thinking were alike futile. For, as a sign of what is going on within, the respiratory quotient is absolutely valueless."

The line of evidence offered by Professor Barnes is particularly applicable in this connection, since it corresponds in a measure with that of Bohr, Haldane and Lorrain Smith, and others, in respect to the pulmonary process: "Von Frey and Gruber[70] showed that in a dog's muscle, with artificial circulation, contractions are accompanied by an increase in the carbon dioxide added to the blood, but they found this increase variable (46-10 per cent.) *and less than the corresponding absorption of oxygen*, so that the respiratory ratio became lowered during contraction. Tissot[71] showed that the production of carbon dioxide in excised muscles was increased if the muscle were killed by heat or were fatigued by prolonged stimulation. The output of carbon dioxide in such cases *was not related to the rate of absorption of oxygen.* Six years ago Fletcher,[72] using Blackman's apparatus, the most intricate and accurate apparatus yet devised for following gaseous exchanges, showed that the evolution of carbon dioxide from excised frog's muscles is *independent of the amount of oxygen taken up during the period.*

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[69] C. R. Barnes: Science, vol. xxi, No. 529, p. 241, 1905.
[70] Von Frey and Gruber: Dubois-Reym. Arch. f. Physiol, S. 533, 1885.
[71] Tissot: Arch. de phys., T. vi, p. 838, 1894, and *Ibid.*, T. vii, p. 641, 1895.
[72] Fletcher: Jour. of Physiol., vol. xxiii, p. 10, 1898.

He distinguished, in the production of carbon dioxide, first, a short period (about six hours), which he thinks dependent upon the presence of oxygen; and second, a long-continued evolution of carbon dioxide 'due to chemical processes occurring spontaneously within the muscle, in which complex molecules are replaced by simpler ones, with the conspicuous results of the appearance of [sarcolactic] acid and of free carbon dioxide.' He adds: 'Under suitable conditions the occurrence of active contractions in an excised muscle is *not* accompanied by an increase in the rate at which carbon dioxide is yielded by the muscle,' though oxygen is abundantly supplied then by the blood."

"A great number of researches of the same tenor can be found in botanical literature," continues the author. "A single example must suffice. In an elaborate paper, Purjewicz[73] shows that the variations in the carbon dioxide produced and the oxygen absorbed during a given period under various conditions *are not parallel,* the amount of *carbon dioxide ranging within far wider limits than the oxygen.* Thus, the carbon dioxide varied from 0.14 to 120 per cent. of the average; the oxygen varied from 0 to 48 per cent. of the average. Purjewicz, indeed, expressed his conviction that the respiratory ratio has no value as indicating the actual course of respiration, and would separate the taking up of oxygen and the production of carbon dioxide as two processes indirectly related."

This evidence speaks for itself. There is no more correspondence between the oxygen intake and the CO_2 output in the tissues than there is in the pulmonary process. What is there, however, to replace oxidation?

Armand Gautier,[74] professor of physiological chemistry in the Faculty of Paris, as far back as 1881 called attention to the fact that the truly active and living portion of our cells (the nucleus and protoplasm) carried on its functions without the direct participation of free oxygen, and that it was only outside, as it were, of the protoplasm itself and at the expense of its products, that the combustion phenomena occurred. To this extraprotoplasmic combustion he also ascribed the greater part of the body's heat and energy—the phenomena which, owing to their prominence, had alone attracted the attention of physiologists. Indeed, analogy could not but suggest, he thought, the direct participation of oxygen in the intraprotoplasmic processes. Surrounded as it was, *intus et extra*, by oxygen, the animal organism logically suggested itself as the seat of a gradual though ceaseless combustion capable of supplying its heat and power. Gautier showed, however, that the protoplasm of our tissues carries on a function similar to the respiratory process of *anaerobic* bacteria, though unlike the latter, it cannot, from simpler materials, ammoniacal salts and a few other mineral salts, elaborate albuminoid substances. But apart from the fact that it requires the latter ready-made, as it were, it is able to modify them, *build them up* in a complicated fashion and simplify them again without direct oxidation of the materials involved in the process.

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[73] Purjewicz: Jahr. wiss. Bot., Bd. xxxv, S. 573, 1900.

[74] Armand Gautier: "La chimie de la cellule vivante," Paris, 1881.

Evidence to the same effect is contributed by Barnes: "Pflüger, in the early seventies," says this author, "discovered what seemed a peculiar form of respiration. He found that a frog put into a *vacuum* continued to give off carbon dioxide; and presently the same phenomenon was observed by Pfeffer and others in plants." He also remarks in the same connection: "Plainly the changes that were going on within the organism which enabled it to give off carbon dioxide when no free oxygen was to be had could only be a rearrangement of atomic groups within the molecule and the formation of products which were simpler than those from which they arose." These are adduced by the author as examples of *anaerobic* respiration. After submitting additional testimony, he states that "the analogy between anaerobic respiration and *fermentation* has been suggested early—even by Pasteur—and has thus been growing closer with each added bit of knowledge." Morat and Doyon,[75] in their recently published treatise, also state that "the view that the process which in the human organism provokes a rise of temperature involves the presence of *oxidizing ferments*, is being increasingly accepted"; the present trend being that *"fermentation is the prevailing chemical process in living beings."*

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[75] Morat and Doyon: "Traité de physiologie," Paris, 1899-1904.

This coincides with Howell's reference to the great probability that "eventually it will be shown that the oxidations in the body are effected by the influence of oxidases or peroxidases acting singly or in combination or in sequence with the hydrolytic enzymes." If, however, we eliminate therefrom the word "singly" which implies direct oxidation—a fallacy we have just seen—and the words "in sequence," which can only be applicable to catabolism, leaving only "*in combination,*" we will be brought within the precincts of demonstrated facts. Indeed, as will be shown in succeeding chapters, there is abundant evidence to the effect that in the tissues as well as in the alimentary canal, the oxidizing substance, or oxidase, acts in combination with hydrolytic enzymes. We have already seen, in the preceding section, that even in invertebrates there are two different substances in the body fluids which respond to the guaiac test: the oxidase, which remained active up to the boiling point, and another which was invariably destroyed "between 50° and 60° C." The identity of the latter suggests itself when we recall that while trypsin is found in all cells, its activity, as stated by Moore,[76] "increases, according to Roberts, with rising temperature, until 60° C. is reached, and then rapidly falls."

In what form does the oxidizing substance take part in this combination? We are no longer dealing with oxygen simply liberated by the red corpuscles, as taught in text-books, but with a substance dissolved in the blood—that which reacts to the guaiac test. As shown by Jolles,[77] the oxidase-catalases (found by Loew, we have seen, in the fluids of all animals and plants studied) are colloid, and are in solution in the blood. Jolles noted, moreover, that they showed, as previously stated, a striking characteristic, *viz.*, that their activity was in definite relation to the number of red corpuscles present. Now, in the first volume (page 715), I had previously shown that droplets derived from the red corpuscles, traced by Hirschfeld from the interior of these cells to the periphery and, through a minute aperture in the latter, to the surrounding plasma, were minute drops of *oxidizing substance*—the so-called blood-plates, platelets, or hæmatoblasts of as many authors, who had not discovered their true identity. Jolles thus not only contributes additional testimony to the presence of an oxidizing substance in the plasma, but he emphasizes a fact I had previously pointed out, viz., that it was through the red corpuscles that the blood-plasma was kept supplied, not with oxygen as now taught, but with its oxidizing substance or oxidase.

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[76] Moore: Schäfer's "T. B. of Physiol.," vol. i, p. 237, 1898.
[77] Jolles: *Loc. cit.*

With what substance known to be present in the red corpuscles does this oxidizing colloid correspond? Gamgee, we have seen in the preceding section, states that "it may be assumed that hæmoglobin exists in the blood corpuscles in the form of a compound with a yet unknown constituent of the corpuscle." Elsewhere, however, he also writes that under the influence of various chemical agents, hæmoglobin "undergoes a decomposition of which the chief products are an *albuminous substance* or substances, *and* a *coloring matter* which contains the whole of the iron originally present in the oxyhæmoglobin or hæmoglobin decomposed." The albuminous substance is evidently the "unknown constituent" referred to above, since he likewise remarks: "As to the true nature of the albuminous residue, we have very little knowledge."

It becomes a question, however, as to which of the two bodies mentioned, the albuminous substance or the coloring matter, is the one capable of leaving the corpuscle, since "coloring matter" suggests that it might be the oxidizing substance. But Gamgee[78] says in this connection: "The coloring matter of the red corpuscles is not extracted from them by the *plasma;*" Schäfer, moreover, states that "it is indiffusible through the unaltered envelope of the corpuscle." It is self-evident, therefore, that it is the albuminous constituent of hæmoglobin that is secreted in droplets by the red corpuscles.

Finally, is the albuminous constituent of hæmoglobin secreted by the red corpuscle the oxidizing substance? Were hæmatin to leave the corpuscles at all, it could not fulfill the rôle of oxidizing substance, for as shown by Hoppe-Seyler (cited by Gamgee[79]). "perfectly pure solutions of hæmatin are quite unaffected by reducing agents." Nor is hæmoglobin, *i.e.*, hæmatin and its albuminous moiety conjoined, endowed with the properties of the oxidizing substance, since, as shown by Piéri and Portier,[80] a solution of this pigment, when tincture of guaiac is added thereto, turns a muddy-red. The oxidizing substance can only be, therefore, the albuminous moiety which is extracted from the corpuscles by the plasma. We have seen that, as shown by Jolles, the activity of the oxidase-catalase is marked in proportion as the number of these cells is great; and also that as stated by Seifert,[81] a solution of human blood becomes in the course of a minute or two, intensely blue, and that this test prevails even when hæmin crystals cannot be obtained.

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[78] Gamgee: *Loc. cit.*, p. 189.
[79] Gamgee: *Loc. cit.*, p. 252.

Summarizing this evidence, and pending additional testimony, we may conclude: (1) *that an exchange of gases does not occur in the tissues any more than in the pulmonary alveoli;* (2) *that tissue metabolism or "respiration" is not due to combustion or oxidation of the tissues;* (3) *that tissue metabolism is due to a process of fermentation in which the oxidizing substance (oxidase, catalase, etc.) takes part;* (4) *that the oxidizing substance required for this function is supplied in the form of droplets (the so-called "blood-platelets" or "hæmatoblasts") by the red corpuscles;* (5) *that the oxidizing substance is the albuminous constituent of hæmoglobin.*

THE RED CORPUSCLES AS STORAGE-CELLS FOR THE OXIDIZING SUBSTANCE.

How is the oxidizing substance held within the red corpuscles pending its gradual distribution? This question brings to light another obscure feature of the problem. Howell,[82] for instance, says: "The point that remains uncertain is the condition in which the hæmoglobin exists within the corpuscle. It is evidently not in solution, since the amount present is too great to be held in solution in the corpuscle, and moreover, even a thin layer of corpuscles is far from being transparent." The answer to this is embodied to a great extent in the data submitted in the foregoing pages: hæmatin is a permanent resident of the red corpuscles; the oxidizing substance only remains within its precincts until a substance having a very marked affinity for its oxygen "extracts" it, in the form of droplets—the minute "blood-platelets." These, as emphasized in the preceding section, are in reality droplets of oxidizing substance, *i.e.*, of oxygen-laden adrenal secretion. As the latter leaves the adrenals in the form of colloid granules and is absorbed by the red corpuscles, the hæmoglobin in the cells meets the conditions defined by Howell: the 94 per cent. of oxygen-laden adrenal secretion they contain besides their hæmatin (which gives the blood its red color) is not in "solution;" it is composed of, hyaline masses sufficiently viscid when secreted by the adrenals to have suggested the term "protoplasmic masses" to Gottschau.[53] Indeed, as stated by Landois,[54] hæmoglobin "is a colloidal substance."

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[80] Piéri and Portier: *Loc. cit.*
[81] Seifert: *Loc. cit.*
[82] Howell: *Loc. cit.*, p. 385.

Again, text-books of physiology teach that it is the iron of the hæmoglobin that takes up the oxygen of the air. We have seen, however, that in all the higher animals the substance which fulfills this function is the albuminous portion of hæmoglobin, that which contains *no* iron. This is further shown by the fact that it is this albuminous body which in the blood fulfills the rôle of catalytic or "oxygen transmitter," a rôle as clearly carried on in plants and invertebrates, in which no hæmatin is present, as it is in animals supplied with this iron pigment. We have seen, also, that it is the substance which is *outside* the red corpuscles, this same albuminous substance, which turns guaiac blue; it is obviously not the hæmatin, since this pigment remains *within* the corpuscles. Finally, if the iron-laden hæmatin were the substance which absorbs the oxygen of the air to supply the tissues, it should also be capable of oxidizing guaiac, *i.e.*, of turning it blue; but it does not; even when mixed with the albuminous substance it turns guaiac a muddy-red. Finally, the albuminous constituent is evidently the familiar carrier of oxygen, oxyhæmoglobin, for as stated by Hammarsten,[55] the substance has "a direct action upon tincture of guaiacum."

This apparently leaves the hæmatin without function, since the only rôle ascribed to it at present is that of taking up the oxygen of the air. Its history suggests, however, that it is endowed with an important though different rôle. Indeed, we have seen that hæmoglobin occurs in relatively few invertebrates, whereas it is present in practically all vertebrates, *i.e.*, at a stage of the animal scale where the blood's volumetric capacity must be greatly increased to satisfy the needs of greater aggregates of cell colonies such as those of which the higher animals are composed. In the preceding section I termed the red corpuscles "storage-cells." Indeed, their advent coincides with a time when, although hæmoglobin is present, its mere dissolution in the blood fluids—as it is in some Annelides—would fail to supply enough oxygen to sustain all the vital functions of the organism. Griffiths,[86] for instance, says: "In the higher animals the corpuscles are of two kinds, red and colorless; but in the Invertebrata there are, as a rule, only colorless corpuscles." A rôle such as that I ascribe to the red cells, therefore, is a logical feature of animal evolution, since by storing a large quantity of the oxygen-laden adrenal secretion or oxidizing substance, these cells meet the needs of advanced development. This involves, however, the presence, in the corpuscle, of a body capable of anchoring the oxidizing substance. Hæmatin is not only endowed with the properties required to fulfill this rôle, but there is in the red corpuscle no other substance to assume it.

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[53] Gottschau: *Loc. cit.*

[54] Landois: *Loc. cit*, p. 51.

[55] Hammarsten: "Text-book of Physiol. Chemistry," fourth edition, p. 169, 1904.

That hæmatin has considerable affinity for oxygen is sufficiently emphasized by the fact that physiologists have long held and now teach, that its iron (Howell[87] states that hæmatin "contains all the iron of the original hæmoglobin molecule") combines with the oxygen of the air, to carry it to the tissues. Given, therefore, a substance such as the *oxygen-laden* adrenal secretion in the blood-stream, and coincidently red corpuscles containing little else than hæmatin, after circulating in the whole body this hæmatin should reduce the oxygen-laden adrenal secretion—provided the hold of the latter upon its own oxygen is sufficiently loose. We have seen, however, that such is not the case, and that the affinity of the adrenal secretion for oxygen is very marked. Hæmatin does not deprive the adrenal secretion of its oxygen, but through its own affinity for the latter draws *within the corpuscle* both this gas and the adrenal secretion. The latter, after its exposure to the air of the alveoli being, as we have seen, the albuminous constituent of hæmoglobin, it serves, on entering the corpuscle and combining with the hæmatin, to build up the hæmoglobin molecule. The hæmatin is evidently capable of thus causing an enormous proportion of the oxygenized adrenal secretion to enter the cell, for the albuminous portion of hæmoglobin represents 94 per cent. (Gamgee) of the whole. This clearly points to hæmatin as the agent which causes accumulation of the oxidizing substance in the red corpuscle and to the latter as a storage-cell.

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[86] Griffiths: *Loc. cit.*, p. 125.
[87] Howell: *Loc. cit.*, p. 390, 1905.

Evidence to this effect is also afforded by the fact that such a function accounts for the existence of the albuminous component of hæmoglobin. We have seen that Gamgee characterized this body as the "unknown constituent of the hæmoglobin molecule." The iron of the hæmatin being solely credited with the rôle in respiration ascribed to hæmoglobin as a whole, this "unknown constituent," though it represents *94 per cent.* of the entire molecule is devoid, according to present teachings, of all function! Again, as Hammarsten[88] says, hæmoglobin "occurs only in very small quantities in arterial blood, in larger quantities in venous blood." Why should such be the case if the iron of the hæmatin alone carries on the respiratory process? The excess of hæmoglobin in the venous blood—which necessarily applies to the albuminous portion, since the iron does not leave the corpuscles—is another feature left in abeyance by the prevailing teachings. With the red corpuscles as storage-cells, however, the reason for this becomes self-evident: In arterial blood the albuminous portion of the hæmoglobin, *i.e.*, the oxygenized adrenal secretion, is stored in the corpuscles; gradually, as it leaves these cells in droplets, we have seen, to circulate in the *minute capillary networks of the cellular elements into which the red corpuscles do not penetrate*, it passes on, as a worn-out substance, to the veins. Briefly, in the arterial blood, it is stored in the corpuscles, while in the venous blood it is free—though deprived of oxygen.

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[88] Hammarsten: *Loc. cit.*, p. 170.

It becomes a question now as to where the red corpuscles are charged, as it were, with their oxygen-laden albuminous constituent, *i.e.*, their oxyhæmoglobin. In the first volume (page 145), I submitted the following conclusions: "(1) When the secretion of the adrenals reaches the pulmonary alveoli, it absorbs oxygen from the air and forms with the latter a compound or 'oxidizing substance.' (2) A part of this oxidizing substance is absorbed by the hæmoglobin of the corpuscles and the balance remains in the blood-plasma." All the evidence collected since has only served to confirm these conclusions.

The course of the adrenal secretion from the adrenals to the lungs having been given in detail in the second section of this chapter (page 806), the changes it undergoes when it reaches the alveoli need alone be reviewed in the present connection.

The need of a secretion to account for the respiratory process pointed out by Bohr and subsequently defended by his collaborator, Henriques, Haldane and Lorrain Smith, and Harley, has steadily gained ground of late. Pembrey, in a subsequent (1906) publication,[89] after a careful review of the respiratory process, concludes: "The body of evidence has thus been steadily increasing in favor of the secretory theory, especially as regards the absorption of oxygen." We have seen, however, that for want of a known secretion to account for the phenomena witnessed, Bohr assumed that the lungs themselves supplied the secretion—a view sustained in no way by experimental facts. We have seen, on the other hand, that my own view that the secretion of the adrenals fulfills this function is backed by very strong testimony from whatever direction the question is considered, and that physiologists have confirmed it.

Once in the close capillary network of the alveoli, the adrenal secretion is only separated from the air they contain by an extremely thin layer composed of delicate alveolar membrane and its alveolar epithelium, which together are barely 0.001 millimeter thick. Indeed, according to Böhm, Davidoff and Huber,[90] the capillary network, "which is extremely fine," is "sunken into the epithelium." Now it is *in these extremely*

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[89] Pembrey: Hill's "Recent Advances in Physiol. and Bio-Chemistry," p. 549, 1906.

[90] Böhm, Davidoff and Huber: "Text-book of Histology," second edition, p. 316, 1905.

fine capillaries that the red corpuscles containing the hæmatin meet the adrenal secretion. Both being reducing agents, they would simultaneously combine with the oxygen of the alveolar air and remain apart were it not for an important fact, *viz.*, that the adrenal secretion, besides being free in the blood, is much more energetic as a reducing agent than the hæmatin within the red corpuscles. As a result, the secretion alone absorbs the oxygen of the air through the delicate alveolar membrane, and the blood in the capillary network is thus constantly saturated, so to say, with oxygen-laden adrenal secretion. It is at this stage that the corpuscular hæmatin comes into play. The red corpuscles—each of which, as stated by Howell, "forms a meshwork or spongy mass"—being surrounded by this blood, their hæmatin absorbs oxygenized secretion until replete, and ready, therefore, to carry on their active function as constituents of the arterial blood, laden as they are with oxyhæmoglobin.

That a reducing agent actually exists in the lungs was emphasized by the labors of Bohr, Haldane and Smith, and others. Garnier,[91] twenty years ago, showed that a solution of ultramarine blue was decolorized when sprayed into the lungs. This can only be produced by a powerful reducing agent. Carbonic acid and taurin, the only two possible components of the alveolar fluids which might act as such, failed invariably to produce such an effect on the solution. Pembrey[92] also writes: "A still further piece of evidence in favor of the secretory theory is the great capacity of the pulmonary tissue to *reduce* alizarin-blue when, as in Ehrlich's experiments, it is injected into the living body, and air is still passing in and out of the lungs."

That this reducing agent is the adrenal secretion is shown in various ways. Oxyhæmoglobin is "readily decomposed," as stated by Hammarsten,[93] by alkalies. Moore and Purinton[94] and others emphasize the fact that the active substance of the adrenals is rapidly destroyed by alkalies. Hammarsten also says that "oxyhæmoglobin is insoluble in ether, chloroform, benzene and carbon disulphide." Vulpian[95] found the expressed juice of the adrenals insoluble in ether and benzene.

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[91] Garnier: C. r. de l'Acad. d. sci. de Paris, July 26, 1886.
[92] Pembrey: *Loc. cit.*, p. 549.
[93] Hammarsten: *Loc. cit.*, p. 169.
[94] Moore and Purinton: Amer. Jour. of Physiol., vol. iii, p. xv, 1900.
[95] Vulpian: C. r. de l'Acad. d. sci. de Paris, Sept. 29, p. 663, 1856.

Moore[96] states that the adrenal active agent is insoluble in ether, chloroform and carbon disulphide. Throughout the various stages of organic life, we have seen, the oxidizing substance, *i.e.*, the oxyhæmoglobin, resists all temperatures up to the boiling point. Cybulski,[97] Moore, and others observed that boiling alone annulled the activity of the adrenal extractives. In other words, the chemical properties of the adrenal secretion are similar to those of free oxyhæmoglobin, the product it becomes, as I pointed out in the first volume, after traversing the alveolar capillaries.

Griffiths states that in *Annelida* the hæmoglobin is dissolved in the fluid Huxley called "respiratory blood," and "does not belong to the corpuscles." Nor does it in man, in whom these corpuscles act only as storage-cells.

This evidence seems to me to warrant the following conclusions: (1) *that it is not the iron of the hæmoglobin as now taught which combines loosely with the oxygen of the air to carry it to the tissues;* (2) *that this function is fulfilled by the oxidizing substance alone;* (3) *that the red corpuscles are storage cells for the oxidizing substance, i.e., the oxygenized adrenal secretion;* (4) *that the corpuscular hæmatin, owing mainly to its iron, is the substance which in the corpuscles acts as storage material;* (5) *that the affinity of its iron for oxygen causes it to combine loosely with the oxygen of the oxidizing substance, as fast as the adrenal secretion is being converted into the latter in the alveolar capillaries;* (6) *that this process entails the absorption into the red corpuscles of all the oxidizing substance they can accommodate;* (7) *that the red corpuscles do not, as now taught, supply free oxygen to the tissues through the intermediary of the plasma;* (8) *that droplets of oxidizing substance are abstracted from the red corpuscles, when any substance having greater affinity for its oxygen than the hæmatin appears in the blood-stream;* (9) *that it is the albuminous oxidizing substance (oxyhæmoglobin) itself which is absorbed by the tissue-cells.*

To sustain adequately these conclusions, however, it is necessary to show that the oxidizing substance is present in all parts of the organism and that its chemical properties coincide wherever found with those of the adrenal secretion.

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[96] Moore: Jour. of Physiol., vol. xvii, p. xiv, 1894-95.
[97] Cybulski: *Loc. cit.*

THE ADRENAL SECRETION AS THE CONSTITUENT OF HÆMOGLOBIN WHICH, WHEN OXIDIZED, PRODUCES BRONZING.

As the albuminous constituent of hæmoglobin, the secretion of the adrenals must necessarily invade all tissues. We have additional evidence to this effect in the pathology of Addison's disease, and particularly in that of its characteristic symptom, bronzing, which, as is well known, may invade the entire surface of the body and all exposed mucous membranes. We are again, however, brought face to face with an unknown factor in this connection, *viz.*, the true identity of the bronze pigment and its origin. Indeed, Hammarsten[98] says that "so little is known about the structural products of melanins or melanoids that it is impossible to give the origin of these bodies.". In a special study of these pigments, Walter Jones[99] also states that "they have been the subject of a number of researches of chemical nature, yet for some reason these researches have been so fruitless that at the present time we are not in a position even to define a melanin in a chemical sense; in fact, we are not all agreed as to what chemical elements are necessary constituents of the melanin molecules."

Alezais and Arnaud,[100] Marino-Zucco,[101] and Boinet,[102] found dark pigment in various organs after injuring or removing the adrenals. In Boinet's experiments this pigment proved to be identical with "bronze" pigment obtained from the skin, mucous membranes and other structures derived from two fatal cases of Addison's disease. As I pointed out in the first volume, bronzing occurs in this affection only when the lesion of the adrenals is *far advanced*, each of these organs (an indication of their important physiological function) being supplied, as shown by Langlois, Gourfein and others, with ten or eleven times the quantity of medulla required to sustain life. Lesions may thus be found *post-mortem* in the adrenals and no bronzing occur during life, merely because the local changes are not sufficiently advanced, while, conversely, a lesion of the nervous or vascular supply of the adrenals may so inhibit their functions, without entailing discernible local changes, as to cause marked bronzing. Under these conditions, any advanced lesion of the adrenals should give rise to bronzing irrespective of Addison's disease. Several such instances have been reported by E. Sergent and Leon Bernard[103] and others, besides those referred to in the first volume of this work.

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[98] Hammarsten: *Loc. cit.*, p. 592.

[99] Walter Jones: Amer. Jour. of Physiol., vol. II, p. 380, 1899.

[100] Brown-Séquard: C. r. de la Soc. de biol., 1892.

[101] Marino-Zucco: Arch. Ital. de Biol., vol. I, 1888; and Riforma Medica, vol I, p. 759, 1892.

[102] Boinet: Marseille méd., Apr. 15, 1896.

In the first volume, I also stated (page 93) that bronzing was attended with "hæmoglobin disintegration." The pigment found by Boinet in his decapsulated rats, and corresponding to the "bronzing" pigment, presented microscopically all the characters of hæmatoidin, a substance also found in old blood extravasations and in apoplectic clots, and which, as stated by Gamgee, is "certainly derived from *hæmoglobin*." Melanin "may be uniformly regarded," according to Charles,[104] "as a derivative of the blood pigment." In a recent work, E. C. Hill[105] also states that "it is derived from the blood pigment."

Chittenden and Albro,[106] however, state that the presence of *sulphur* "in very appreciable amounts constitutes one of the reasons for the belief that these substances have their origin in some proteid antecedent, while the *absence of iron*, in most cases, *excludes* the view that they originate from the blood pigment." That such is not the case, however, may be shown by the evidence these investigators adduce to support their conclusion. Hæmoglobin, we have seen, may be split into hæmatin, which contains all the iron, and the albuminous body, *i.e.*, the oxidizing substance. Since, as shown, all the iron remains in the corpuscles, it is self-evident that melanin may not contain iron and still form part of the hæmoglobin molecule. As stated by Chittenden and Albro, melanin contains sulphur. This necessarily refers it to the *albuminous* constituent of hæmoglobin also, since Gamgee states that "the *sulphur* belongs to the albuminous part of the molecule." Again, the presence of this element indicates that "hæmoglobin belongs to the *proteid* compounds" (Halliburton[107]), and inasmuch as it is the albuminous body which contains the sulphur, it is this body which is of proteid nature. It is evident, therefore, that Chittenden and Albro's conclusion that melanin does not originate from blood-pigment, cannot hold.

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[103] Sergent and Bernard: Arch. gén. de méd., p. 27, July, 1899.
[104] Charles: "Elements of Physiol. and Path. Chemistry," p. 284, 1884.
[105] Hill: "T. B. of Chemistry," p. 374, 1903.
[106] Chittenden and Albro: Amer. Jour. of Physiol., vol. ii, p. 291, 1899.
[107] Halliburton: Schäfer's "T. B. of Physiol.," vol. i, p. 27, 1898.

Melanin remaining, therefore, a constituent of hæmoglobin, *i.e.*, the albuminous constituent I have identified as the oxidizing substance, there is good ground for the belief that it contains adrenal secretion. This postulate acquires additional strength in view of the cardinal rôle I have ascribed to this secretion in tissue metabolism, and the fact that the skin-fluids—of batrachians at least—show by their positive reaction to the guaiac test that the oxidizing substance is present in them.

Points of analogy between hæmoglobin and melanin on the one hand, and the oxidizing substance considered as active through its adrenal secretion, on the other, are discernible in various directions. Much of the chemical work done on the melanins, however, is misleading in that possible sources of error were not taken into account. "If we consider for a moment the *methods* which have been employed for the isolation and purification of the pigment," says Walter Jones, "and at the same time grant that these substances may be *very sensitive* to the action of chemical reagents, and that it is also within the bounds of possibility that the composition of the pigment, like that of hæmoglobin, is different for different animal species, we will then be in a position to appreciate just such a discordance of analytical results as that which actually exists." This remark applies forcibly to the question in point, for if melanin should prove to be the catalytic body it now appears to be, the promiscuous use of reducing and oxidizing agents cannot but have introduced contradictory results at every turn.

The marked sensitiveness to the action of reagents to which Walter Jones alludes is confirmed by Abel and Davis,[108] who found that the composition of melanins isolated by them was "easily subject to change by subsequent treatment of the material with alkalies." This same sensitiveness attends the albuminous constituent of hæmoglobin; thus Gamgee refers to it as being "characterized by remarkable instability." Strong alkalies that cause the hæmoglobin molecule to break down also annul the activity of adrenal extractives: "The use of alkalies," write Moore and Purinton,[109] "should be avoided in any method devised for the isolation of the active substance, since the activity is thereby rapidly destroyed." As Moore[110] has previously stated that alkalies supplemented by heat also caused oxidation of the reducing agent in adrenal extract, melanin should likewise actively take up oxygen through alkalies, if the kinship really exists: Jones refers to several experiments in which ammonium permanganate was used as oxidizing agent, at temperatures between 0° and 5° C. "Even under these conditions," says this chemist, "the permanganate is almost immediately decolorized, showing that in alkaline solution the *pigment is oxidized with the greatest ease.*"

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[108] Abel and Davis: Jour. of Exper. Med., vol. i, p. 361, 1896.

This not only clearly connects melanin with the adrenal secretion, but it does so with the adrenal secretion as a constituent of the albuminous body. Indeed, we have seen that the sulphur in hæmoglobin belongs to the latter only, and that, as shown by Sieber[111] and Hirschfeld,[112] melanin also contains sulphur.

Still, if melanin contains the adrenal secretion, the latter should also contain sulphur. The active principle of the adrenals contains no sulphur, the formula of adrenalin being $C_9H_{13}NO_3$. The *secretion,* however, which embodies the active principle, contains this element. Manasse[113] found it in the glandular substance. Metzger[114] also obtained it from adrenal precipitates. Gurber[115] found that adrenal substance gave off sulphur in the form of sulphuretted hydrogen when heated to 140° C. Sulphuretted hydrogen was also obtained by Schmiedeberg,[116] from melanin.

Additional evidence is afforded by the fact that melanin is precipitated from its solutions by agents which act similarly on adrenal extracts. Just as Vulpian, fifty years ago, found the expressed juice of adrenals insoluble in alcohol, ether and benzene, to which list others have added chloroform, so does Arthur Jones refer, in his recently published paper, to an acid preparation (adrenalin is not destroyed in acid solutions) of melanin obtained by him, as being "insoluble in alcohol, ether, benzene, acetic ether and chloroform."

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[109] Moore and Purinton: Amer. Jour. of Physiol., vol. iii, p. xv, 1900.
[110] Moore: Jour. of Physiol., vol. xvii, p. xiv, 1894-95.
[111] Sieber: Archiv f. exp. Path. u. Pharm., Bd. xx, S. 363, 1886.
[112] Hirschfeld: Zeit. f. physiol. Chemie, Bd. xiii, S. 418, 1889.
[113] Manasse: Zeit. f. physiol. Chemie, Bd. xx, S. 478, 1895.
[114] Metzger: Inaug. Dissert., Giessen, 1897.
[115] Gurber: Sits. d. physik. med. Gesellsch., Wurzburg, Bd. xxix-xxx, S. 139, 1897.
[116] Schmiedeberg: Arch. f. exp. Path. u. Pharm., Bd. xxxix, S. 2, 1897.

Again, several chemists have assimilated the chromogen of the adrenals to pyrocatechin, a substance found in mucin, the urine, etc., and which, precisely as Vulpian observed in the case of adrenal juices, gives an emerald green color with ferric chloride and other characteristic tests. Krukenburg[117] suggested that the chromogenic substance contained pyrocatechin. Brunner[118] found that an alcoholic extract of adrenals gave practically all the reactions of this body. Mühlmann[119] likewise concluded that pyrocatechin was present in the adrenals, and observed that just as pyrocatechin became brown when exposed to light or to the action of alkalies, so did adrenal extractives. He held, therefore, that, inasmuch as the latter were powerful reducing agents, the adrenal secretion on entering the arterial blood became oxidized and turned brown. This, he thought, accounted for the bronzing of Addison's disease. That this view is erroneous is obvious; for our arterial blood would, in that case, be oxidizing constantly the adrenal secretion irrespective of the presence of Addison's disease. Again, since this disease is associated with a destructive lesion of the adrenals, it would tend to prevent bronzing, rather than cause it.

Yet, Mühlmann's conception, as interpreted from my standpoint, embodies the main feature of the process of bronzing, *i.e.*, that it is *a product of the adrenals which, on becoming oxidized, turns brown* in Addison's disease. What is the nature of this process?

We have not far to seek. Since bronzing occurs only in the advanced stage of Addison's disease, and the pigment of bronzing appears in the blood after removal of both adrenals, it is evident that we are dealing with a general lowering of the blood-pressure such as that which occurs, as shown by Strehl and Weiss, when the adrenal veins (through which the secretion reaches the general circulation) are clamped. This means relaxation of all the vessels, a torpid circulation and passive infiltration into the cutaneous elements of blood-plasma containing oxidizing substance. All functional processes being torpid, absorption of the exudates is delayed and may even be arrested in tissues supplied by the diminutive capillaries of the surface, where the circulation is at best sluggish. It is here that the pigment accumulates, *i.e.*, in the epidermal layers, where it may become oxidized by what oxygen the fluids in which it bathes may contain or oxygen derived from the air. The presence of sulphur, iron and other elements in the surrounding tissues may so influence the process as to give rise to various hues—those witnessed in various cutaneous disorders. A similar process may occur in any organ.

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[117] **Krukenburg: Archiv f. path. Anat. u. Physiol., Bd. ci, H. 3, S. 542, 1885.**
[118] **Brunner: Schweizer Wochen. f. Pharm., Bd. xxx, S. 121, 1892.**
[119] **Mühlmann: Deutsche med. Wochen., Nu. 26, S. 409, 1896.**

We have seen in the third section that exposure of oxidase to the air was followed by a similar process and that juices derived from the skin of batrachians first became brown, then black. Osler[120] states that in Addison's disease "the coloration ranges from a light yellow to a deep brown or even black." Harlow Brooks's[121] case of extreme anæmia attended with disease of both adrenals, in which there was a "dark brown, *glossy* pigmentation" of the skin also recalls the process of lacquer formation with the oxidizing substance of the latex tree, *i.e.*, laccase, as described by Bertrand. In both these two extremes of organic life—man and plant—the reducto-oxidizing body had ceased to circulate in its normal channels, and, becoming oxidized, was converted into the substance which in man produces "bronzing."

On the whole, the following conclusions seem warranted: (1) *that bronzing is due to an accumulation of melanin in the epidermal layers of the skin;* (2) *that melanin is a compound formed when oxidizing substance, i.e., the albuminous portion of hæmoglobin, has become vicariously oxidized in any organ (hæmatoidin) or in the skin;* (3) *that the constituent of oxidizing substance which becomes oxidized, when melanin is formed, is the adrenal secretion;* (4) *that whereas melanin is formed in any part of the body, the adrenal secretion circulates in all parts of the body.*

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[120] Osler: "Practice of Med.," p. 831, 1898.
[121] Harlow Brooks: Med. Rec., Feb. 22, 1902.

THE ACTIVE PRINCIPLE OF THE ADRENAL SECRETION AS THE ACTIVE AGENT OF THE OXIDIZING SUBSTANCE.

To render all the evidence submitted so far conclusive, the actual presence of the active principle of the adrenals in the oxidizing substance, *i.e.*, the albuminous portion of hæmoglobin, should be demonstrated.

The minuteness of the dose of adrenal that will provoke marked effects suggests that it is as an active principle that it must carry on its important function. "In order to produce a maximal effect," says Schäfer,[122] "a dose of not more than fourteen-millionth of a gramme of the active material per kilo of body-weight is all that is necessary. Now it is certainly true to say that one-fourteenth of this dose will produce some effect, although not, perhaps, a very large one. We thus arrive at the astounding conclusion, that the active principle of the suprarenal capsules, administered in the proportion of not more than one-millionth part of a gramme per kilo of body-weight, which would be equivalent to $^1/_{12000}$ gramme (less than $^1/_{800}$ of a grain) for an adult man, is still sufficient to produce distinct physiological results upon the heart and arteries." The activity of minute doses has been emphasized also by the experiments of Moore and Purinton[123] and Reid Hunt.[124]

Even these diminutive doses perceptibly influence tissue-metabolism. Oliver and Schäfer[125] refer to a slight, transitory "disturbance of the body temperature." When the doses are lethal the latter falls, but after large doses there is a distinct rise. Reichert[126] observed an elevation of 1° F. in rabbits, accompanied by increased metabolism. Lépine[127] states that the increase of blood-pressure is always followed by a rise of temperature. Morel,[128] in four guinea-pigs noted a rise of from $^1/_2$° to 1° C. (0.9° to 1.8° F.). This is controlled by the well-known phenomena that follow removal of both adrenals. Lowering of the temperature was first noted by Brown-Séquard, and since by practically all experimenters. Vassale and Zan-

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[122] Schäfer: "T. B. of Physiol.," vol. i, p. 957, 1898.
[123] Moore and Purinton: Amer. Jour. of Physiol., vol. iii, p. xv, 1900.
[124] Reid Hunt: *Ibid.*, vol. v, p. vii, 1901.
[125] Oliver and Schäfer: Jour. of Physiol., vol. xviii, p. 230, 1895.
[126] Reichert: Univ. of Penna. Med. Bull., Apr., 1901.
[127] Lépine: Semaine méd., Feb. 18, 1903.
[128] Morel: Le progrès méd., Aug. 3, 1903.

frognini[129] *observed it even during the prolonged post-operative life insured by leaving a portion of the medullary substance intact and* *in situ*. Finally, as is well known, hypothermia is a marked symptom of Addison's disease.

If the oxidizing substance, whether linked with the coloring matter as in higher animals, or not, as in the colorless blood of invertebrates, actually contains the active principle of the adrenals, this principle should be found in the blood-plasma. Its presence therein was shown by F. Battelli.[130] As observed by Oliver and Schäfer, Langlois and others, the effects of adrenal extract only last three or four minutes—a fact which led to the belief that it was destroyed in the blood. Such was found by Battelli, however, not to be the case: Normal blood was rapidly centrifugalized. The serum thus obtained was acidulated, subjected to a temperature of 85° C. (which, as we have seen, destroys all active agents except the oxidizing ferment) and concentrated by pressure. One cubic centimeter of this serum invariably raised the blood-pressure. That this was due to adrenal substance was shown by the fact that the concentrated serum was rendered inert by precisely the conditions that affect adrenalin similarly, *i.e.*, oxidation by exposure to the air, and variations of activity on exposure to sunlight, diffuse light and darkness. Quantitative experiments, moreover, showed that "normal *serum* in the dog contains adrenalin in the proportion of 1 in 10,000,000 to 1 in 20,000,000." This is exclusive, of course, of that contained in the hæmoglobin which had remained in the corpuscles.

We have seen that the minuteness of the dose of adrenal extract that will produce distinct physiological effects is referred to by Schäfer as "astounding," its administration "in the proportion of not more than one-millionth part of a gram per kilo of body weight" to an adult man being "sufficient to produce distinct physiological results upon the heart and arteries." In the more recently discovered active principles we have far more powerful agents even than Schäfer employed in his experiments. Indeed, Reid Hunt[131] obtained the following effects with Abel's active epinephrin sulphate:—

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[129] Vassale and Zanfrognini: Riforma Medica, Oct. 31, 1902.

[130] F. Battelli: C. r. de la Soc. de biol., vol. liv, p. 1179, 1902.

[131] Reid Hunt: Amer. Jour. of Physiol., vol. v, p. vii, 1901.

		Rise of blood-pressure
0.083	millionths of a gram per kilo body weight	5 mm. Hg.
0.23	millionths of a gram per kilo body weight	7 mm. Hg.
0.49	millionths of a gram per kilo body weight	15 mm. Hg.
0.69	millionths of a gram per kilo body weight	20 mm. Hg.
1.7	millionths of a gram per kilo body weight	24 mm. Hg.
5.7	millionths of a gram per kilo body weight	60 mm. Hg.

"These results show," according to Hunt, "that epinephrin sulphate is many times more powerful than the *aqueous extracts* of the medulla of the suprarenal obtained by Moore and Purinton." As adrenalin is at least as active as epinephrin sulphate, the proportion of the former active principle found in the plasma by Battelli corresponds with its "astounding" activity, especially when we consider that in Hunt's experiments, the quantities mentioned were *added* to that already present in the blood of the animals used.

The fact that such minute quantities prove active is, from my standpoint, of great practical importance, since, as shown in the first volume, and as will be further emphasized, many of the effects of drugs, poisons, and toxins are in reality due to the fact that they indirectly stimulate the adrenals, and by thus causing these organs to increase the proportion of their secretion in the blood, correspondingly raise the blood-pressure, hasten metabolism, etc.

That the blood-plasma contains the adrenal active principle is shown by considerable experimental evidence.

In the first place, it is evident that as previously shown, the adrenal secretion as the constituent of the oxidizing substance circulates in all parts of the body. This is demonstrated by the additional fact that it is found in *shed* blood in combination with other constituents of the plasma, *i.e.*, in fibrin.

Gamgee, as we have seen, found that very little was known as to the true nature of the albuminous constituent of hæmoglobin, that to which I traced the adrenal secretion. He states, however, that "the most interesting observations on the *albuminous* products of the decomposition of oxyhæmoglobin" were published nearly forty years ago by Kühne,[132] who showed that "when CO_2 is passed through solutions of pure oxyhæmoglobin a flocculent precipitate is thrown down which does not possess, as had been erroneously asserted by A. Schmidt, *fibrinoplastic* properties."

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[132] Kühne: "Lehrbuch," S. 206, 207. 1868.

In the light of later experimental work, however, Kühne's observation is subject to a different interpretation. M. Arthus[133] refers to the blood coagulation as follows: "We know that the conversion of fibrinogen into fibrin, the fundamental phenomenon of coagulation in the blood, is caused by the action of a diastatic agent, fibrin ferment, thrombine, or plasmase, produced by the leucocytes in the blood withdrawn from the vessels." In the first volume I advanced the view that the body which converted fibrinogen into fibrin *extra corpore* was in reality the oxidizing substance and that leucocytes absorbed some of the latter to carry on their own functions. Now Abelous and Biarnès[134] found that *"dilution and a current of carbon dioxide precipitate the oxidizing substance"** from saline solutions of fibrin. This conclusion was based on the fact that when a filtered and very active solution of *fibrin* containing ten per cent. of sodium chloride is diluted with distilled water to seven or eight times its volume, a current of CO_2 passed through it causes the formation of a precipitate. "This precipitate," say these investigators, "treated directly *with tincture of guaiac becomes intensely blue.* Conversely, the liquid from which it was separated remains absolutely inactive." Now, Kühne, as Gamgee says, asserted that the precipitate thrown down by passing CO_2 through solutions of pure oxyhæmoglobin did not possess fibrinoplastic properties. He found also, according to Gamgee, that this precipitate "does not behave as a globulin" and that "it forms long, colorless fibers" resembling connective tissue. It seems plain that his precipitate was simply fibrin. As such it had obviously lost its fibrinoplastic properties and become *a compound of fibrinogen* and *oxidizing substance.*

All this shows that Schmidt was partly right when he concluded that the precipitate in question had fibrin-forming properties. But it proves, moreover: (1) that since fibrin is obtainable from blood drawn from any portion of the body, the oxidizing substance, which turns blue when treated to guaiac, also circulates in all parts of the body, and (2) that since the adrenal secretion is a constituent of the oxidizing substance it circulates likewise in all tissues.

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* The italics are Abelous and Biarnès's own.—S.

[133] M. Arthus: Jour. de physiol. et de path. gén., vol. iii, p. 897, 1901.

[134] Abelous and Biarnès: Arch. de Physiol., T. x, p. 665, 1898.

In the second place, there is no legitimate ground for doubt that, as I have already pointed out, it is the adrenal secretion *in the plasma* which carries on all respiratory processes.

When the secretion leaves the adrenals to reach the vena cava by way of the suprarenal veins, some of it at least must remain in the plasma. Thus Dreyer, whose experiments have been referred to, obtained effects similar to those evoked by adrenal extracts with blood derived from the suprarenal veins and which had been defibrinated and then filtered through muslin. Biedl used blood which had been both defibrinated and centrifugalized, and he specifies that it acted as effectually as the whole blood—a fact which led him to conclude that the "active substance" was "also contained in the serum." The experiments of Battelli referred to above were also performed with *serum*, and it was in this fluid that he found adrenalin. While Biedl used serum from the adrenal vein, Battelli analyzed serum from the general circulation—a fact which indicates widespread distribution of the secretion.

That it is a constituent of the plasma which appropriates the adrenal secretion is further shown by the fact that the proportion of blood-cells in the circulating blood does not influence the respiratory exchanges. Pembrey and Gurber[135] found that these remained the same in rabbits deprived by bleeding of one-half of their blood-corpuscles. As the liquid portion of the blood is restored at the expense of the lymph circulation, the proportion of red corpuscles was reduced one-half. Pettenkofer and Voit[136] have also shown that cases of simple anæmia, in which, therefore, the red corpuscles were greatly reduced in number, absorbed as much oxygen and excreted as much carbon dioxide as healthy men upon a similar diet and at rest. Suggestive in this connection is that this corresponds with Bohr and Henriques's previously mentioned observation that when all the arteries given off by the aorta were ligated, the respiratory exchanges were sometimes *increased*, and that it was only when the inferior vena cava (the sole pathway for the adrenal secretion) was also obstructed that they dropped to a minimum. This plainly shows that it is the adrenal secretion which sustains the respiratory process.

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[135] Pembrey and Gurber: Jour. of Physiol., vol. xv, p. 449, 1894.
[136] Pettenkofer and Voit: Zeit. f. Biol., Bd. v, S. 319, 1869.

Finally, it is evident that all this refers to the *free, i.e., albuminous* portion of the hæmoglobin, for we have already seen that when the guaiac test was applied to a solution in which the contents of the red cells, including the iron-laden hæmatin, had been voided, a muddy-red color appeared instead of the typical blue.

These three cardinal facts being established, the presence of the active principle of the adrenals in the blood-plasma of the entire organism asserts itself, since the *heat* and *solubility* tests correspond with the *color* test (the guaiac blue) at every stage of organic life, *i.e.,* from plant to man.

"We know," write Abelous and Biarnès,[137] "that *heat* enables us to separate two substances from sodium chloride and other neutral salt solutions of fibrin: one substance is precipitated between 56° and 58° C. and another is only precipitated *above* 70°." The nature of the first precipitate is well shown in the following sentence of Schäfer's,[138] concerning blood-coagulation: "A temperature of 56° C. prevents coagulation by precipitating the *fibrinogen* upon which the coagulation depends." Abelous and Biarnès refer to this body as "remaining inactive with guaiac," while the "fluid from which the precipitate had been separated markedly oxidized guaiaconic acid," *i.e.,* gave the blue reaction. "This experiment shows," add the authors, "that in saline macerations of fibrin, the *oxidizing agent* was not the globulin precipitating at 58°, but the globulin precipitating above 70°." What they mean by the latter is explained in the same paper by the statement that "the temperature of 100° C. causes organs [lungs, spleen, etc., and the fibrin] to lose the property of coloring blue the tincture of guaiac, while a temperature of 50° to 60° does not abolish this oxidizing property."

Now, wherever the oxidizing ferment has been referred to in its relations to temperature so far, we have seen that the boiling point (100° C.) at least had to be reached before its activity was destroyed. This was found to be the case with the oxidizing substance of batrachians by Phisalix; of mollusks by Piéri and Portier; of crustaceans by Abelous and Biarnès, and of plants by Bertrand. The last named chemist, for instance, states that the plant ferment laccase "provokes direct oxidation of the bodies upon which it acts," but he also says that "with a boiled solution of laccase, or in the absence of oxygen [thus affirming its identity as a catalytic] it produces no coloration." We must not, however, lose sight of the fact that laccase is an *active principle*, and that it is this principle alone which can withstand temperatures at least up to the boiling point. The same principle doubtless exists in the mollusks studied by Piéri and Portier, since "50° and 60° C." and then 90° were applied in turn to the fluids tested, and their oxidizing activity only ceased when they had been boiled some minutes.

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[137] Abelous and Biarnès: *Loc. cit.,* p. 687.
[138] Schäfer: "T. B. of Physiol.," vol. 1, p. 146, 1898.

A similar resistance to the action of heat is shown by *adrenal extract*. Indeed, it was believed at first that even boiling could not destroy its physiological activity, but Moore[139] showed that it ceased to act when the boiling was continued for three or four hours. Even the adrenals *per se*, as observed by Cybulski, will no longer, after having been boiled, yield an active extract.

That the active principle of the blood's oxidase and that of the adrenals are identical is further demonstrated by the fact that their solubilities likewise correspond.

While Gamgee[140] states that hæmoglobin, which, as well as oxyhæmoglobin, exists "in colored blood-corpuscles in the form of loose or unstable combinations with some other constituent," is insoluble in absolute alcohol, chloroform, benzol, ether and other organic solvents, Vulpian[141] found that the expressed juice of the adrenals was also insoluble in organic solvents, alcohol, ether, benzene, etc., and that this applied to the extracts of *no other gland*. Gautier[142] also refers to the extract as being insoluble in alcohol, ether and chloroform. Gamgee includes carbon disulphide among these agents. Moore states that the active principle of the adrenals is insoluble in ether, chloroform, amyl alcohol and carbon disulphide.

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[139] Moore: Jour. of Physiol., vol. xvii, p. xiv, 1894-95.
[140] Gamgee: *Loc. cit.*, p. 206.
[141] Vulpian: C. r. de l'Acad. de sci. de Paris, Sept. 29, 1856.
[142] Gautier: "Chimie biologique," p. 355, 1892.

The constituent of hæmoglobin which can thus be precipitated from its solutions is evidently contained in its albuminous portion (94 per cent. of hæmoglobin, the remaining 6 per cent. being hæmatin), since it is also precipitated by alcohol as is laccase from its solutions, as stated by Bertrand, and from the extract of gills and palps of mollusks, which contain no coloring matter, as observed by Piéri and Portier. Alcohol precipitated the active substance from fibrin extract—free from hæmatin, of course—in solution, as stated by Abelous and Biarnès. Now, adrenalin, which, as pointed out by Battelli, is widespread throughout the plasma, is precipitated by the same reagents. Takamine, its discoverer, found that it was insoluble in alcohol, ether and chloroform.

Conversely, adrenal extracts were found very soluble in water, by Vulpian, and the hyaline droplets or granules of secretion derived from the adrenals likewise by Manasse.[143] Bertrand found the laccase of plants very soluble in water; the same property belonged to the oxidizing bodies in the crustaceans studied by Abelous and Biarnès. Finally, adrenalin, though very slightly soluble in cold water, is soluble in warm water, and readily so at the temperature of the blood-stream.

The correspondence between the chemical properties of adrenal extracts, adrenalin and other adrenal extractives with those of the active principles of the oxidizing substance or oxidases wherever found thus shows *that a ferment of which the active principle of the adrenal secretion is a type is the active agent in the oxygenation processes of all plants and animals.*

Concluding Remarks.—Pembrey,[144] in the recently published work already referred to, clearly defines the two antagonistic views as to the nature of the respiratory process as follows: (1) "The gaseous exchange between the blood and the alveolar air is due to the relative partial pressure of the gases in the blood and alveolar air, and can be explained according to physical and chemical laws;" (2) "the gaseous exchange takes place in opposition to the known physical and chemical laws, is of a special nature, a vital process akin to the secretion and excretion of glands." As interpreted from the evidence and conclusions submitted in the present work, the second view assumes another aspect:—we are not dealing with processes which in any way stand in opposition to known physical and chemical laws, but with processes in which the relative partial pressure of gases *does not enter at all.*

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[143] Manasse: *Loc. cit.*
[144] Pembrey: *Loc. cit.*, p. 843.

According to this interpretation, it is because the diffusion doctrine is a misapplication of the physical and chemical laws referred to that its sponsors even at these advanced times fail to agree. "So great is the want of agreement and irregularity of the results obtained by different observers with various forms of tonometer," writes Pembrey, an able and impartial reviewer, "that the suspicion arises that there are sources of fallacy in the methods." The chief of these, as I have pointed out, is reduction of the oxygen of the blood during its passage into and through the instrument. Indeed, when Bohr devised one "through which," says Pembrey, "a constant and rapid stream could be maintained," the results were such as to show that "the absorption of oxygen in these cases could not be explained by diffusion." Haldane and Lorrain Smith not only confirmed these results, but in their experiments, "the pressure of the gas in the *arterial blood* [was] *higher in every case.*" *

In the first volume, I pointed out that it was the secretion of the adrenals which took up the oxygen of the air to carry it to the tissues. We have seen in the present chapter that this conclusion was warranted. I may add that at every step of these researches an earnest effort was made to find evidence tending to weaken this conception and that not a single experimental fact was found which did not harmonize with it. That the diffusion doctrine has totally failed in this connection even among its defenders, we have seen. In comparison with this doctrine at least, therefore, the following conclusion stands proven:—

The physiological function of the internal secretion of the adrenals is loosely to combine with the oxygen of the air in the

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* The italics are my own.—S.

pulmonary alveoli and to endow the blood with its oxygenizing properties.

ADRENOXIDASE.—As the term "oxyhæmoglobin" includes the hæmatin of the hæmoglobin molecule as well as its albuminous constituent (the oxidizing substance or oxygenized adrenal secretion), it cannot be used to denote the latter, which alone carries on all oxygenation processes. Nor is the term "oxidizing substance" applicable, since it refers to any agent capable of oxidizing. Hereafter, therefore, I will call this body "*adrenoxidase,*" a term which embodies four salient features: its origin, the adrenals; its general distribution as suggested by "oxidase;" the identity of its active principle not only as a ferment, likewise suggested by "oxidase," but also as a catalytic, a property common to all oxidases.

CHAPTER XIV.

THE ADRENAL ACTIVE PRINCIPLE AS THE FERMENT OF FERMENTS.

ADRENOXIDASE AS A CONSTITUENT OF ENTEROKINASE AND OF TRYPSIN.

Notwithstanding the vast labor devoted to the pancreatic and other intestinal ferments, their nature has remained obscure to this day (1921). Moore,[1] for instance, writes: "Practically nothing is known of the enzymes of the small intestine save their action on foodstuffs, none of them have been obtained in even approximately pure condition, and the fact that they are enzymes rests on the observation (1) that the action is destroyed by boiling and (2) that it takes place under antiseptic conditions." As the oxidizing ferments alone resist heat up to the boiling point; and as Schoenbein[2] found oxidases in all secretions, the likelihood that the adrenoxidase plays an important part in intestinal digestion is very great, especially in view of the fact that all secretions obtain their fluids from the blood. This is further emphasized by the facts that the active principle of adrenoxidase is a catalytic, as we have seen, and that the ferments are known to possess this property. Thus, Moore, after defining the meaning of catalysis, states that "ferment actions are such catalytic reactions."

A zymogen or mother-substance, as is well known, is itself inactive. "The enzymes of the pancreatic secretion are derived from the granules in the cells," says Howell,[3] "but other facts show that the granules do not contain the enzymes as such, but a preparatory material or mother substance to which the name zymogen (enzyme-maker) has been given." Stewart,[4] moreover, states that the "fresh pancreas is devoid of trypsin," but that "it contains a substance which can readily be changed into trypsin; and this substance is soluble in glycerine, for the inert extract becomes active when it is treated with dilute acetic acid, or even when it is diluted with water and kept at the body temperature." Of the manner in which this occurs, however, nothing is known.

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[1] Moore: Schäfer's "T. B. of Physiol.," vol. i, p. 241, 1898.
[2] Schoenbein: Jour. f. prakt. Chemie, Bd. lxxxix, 1863.
[3] Howell: "Amer. T. B. of Physiol.," vol. i, second edition, p. 285, 1900.
[4] Stewart: "Manual of Physiol.," fourth edition, p. 334, 1900.

Recalling some of the properties of adrenal extractives, the process involved in the experiments outlined by Stewart suggests itself. In all processes attended by catalysis water is necessary. Moreover, as shown by Hoppe-Seyler,[5] Nencki[6] and others, fermentative reactions are invariably accompanied by hydration; in other words, as stated by Bunge,[7] "these processes can only take place in the presence of water." Hence, a glycerine extract of pancreatic mother-substance will not act unless water be added to it. Now, we have just seen that such an extract *simply "diluted with water"* becomes active. This applies equally well to the corresponding effect of the dilute acetic acid referred to by Stewart. The water of the acetic acid solution acts in the same manner, but as dilute mineral acids are even more active diluents for the adrenal extractive than water alone, the operation is facilitated, and a very active ferment is obtained.

This entails, however, the need of oxygen. Sakharoff[8] recently showed that oxygen was a *sine qua non* in the action of ferments. Starch-paste containing diastase and heated to 50° C., but covered with a thick layer of boiled oil, produced no sugar, while a similar preparation, minus oil, *i.e.*, exposed to the air, produced sugar. This portion of the fermentative process evidently begins as soon as the ferment is formed in the organ, since Barcroft and Starling[9] state, basing their conclusion on exhaustive chemical and gasometric experiments, that "the pancreatic secretion is accompanied by an increased oxygen absorption," thus confirming Sakharoff's observation.

That a direct connection between oxygen and trypsinogen in the formation of trypsin occurs, was, in fact, shown by Heidenhain over thirty years ago.[10] Indeed, Edkins[11] includes among the conclusions reached by Heidenhain the following: "If an inactive glycerine extract of fresh pancreas be dissolved in sodium bicarbonate, 1 to 2 per cent. passing through it of *oxygen* will cause the same to become active." Moreover, "the converse of the change brought about by the influence of oxygen may also occur, for, through the deprivation of oxygen, activity becomes lost."

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[5] Hoppe-Seyler: Pflüger's Archiv, Bd. xii, S. 14, 1876.

[6] Nencki: Jour. f. prakt. Chemie, Bd. xvii, S. 105, 1879.

[7] Bunge: "Physiol. and Path. Chemistry," second American edition, p. 158, 1902.

[8] Sakharoff: Roussky Vratch, Apr. 24, 1904.

[9] Barcroft and Starling: Jour. of Physiol., vol. xxxi, No. 6, p. 491, 1904.

[10] Heidenhain: Archiv f. d. ges. Physiol., Bd. x, S. 557, 1875.

[11] Edkins: Schäfer's "T. B. of Physiol.," vol. i, p. 552, 1898.

Closely related to the process is the source of the oxygen thus consumed. Barcroft and Starling found that the "increased oxidation" of trypsinogen "takes place irrespective of increased blood-flow through the organ." This confirms a corresponding observation of O. May[12] that "there is no direct relationship between the rate of secretion of pancreatic juice and the extent of the blood supply." It is evident, therefore, that inasmuch as the quantity of blood supplied to the organ is not increased while the absorption of oxygen is, the source of the excess of oxygen must have been the blood itself. "Excess," in this connection, normally entails the presence of *stored* oxygen, or rather, of stored adrenoxidase, and of storage-cells, the red corpuscles, both of which, as I have shown in the foregoing chapter, are available.

The fact that the blood-flow through the organ is not augmented appears to conflict with the memorable observation of Claude Bernard that increased activity of the submaxillary gland is attended by an increased flow of blood through the organ, but as I have shown in the first volume (page 275), the increased flow is not at the expense of the general circulation, but is due to the shifting of a portion of the blood contained in the arterioles of the organ to the capillaries of its secretory elements. The details of the mechanism will be submitted later. The result as to increased blood in the organ remains the same. Indeed, Landois[13] says, referring to the pancreas, that "during the act of secretion the blood-vessels behave like those of the salivary gland after stimulation of the facial nerve; they are dilated, the venous blood being bright red." The direct participation of oxygen in the formation of trypsin is also referred to by the same author,[14] in the following words: "Trypsin results through the taking of oxygen within the pancreas, from a mother substance, zymogen, which collects in the interior of the secreting cells."

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[12] O. May: Jour. of Physiol., vol. xxx, p. 413, 1904.
[13] Landois: "T. B. of Human Physiol.," tenth edition, p. 307, 1905.

The manner in which the adrenoxidase is brought into contact with the pancreatic trypsinogen has been reviewed at length in the first volume. I may repeat, however, my eighth conclusion (page 405), that "the true secreting cells and those of the islands [of Langerhans] being in continuity and surrounding a common lumen (Opie), both bodies—(1) the zymogen, or trypsinogen-forming granules, and (2) the plasma containing the splenic ferment and the oxidizing substance [adrenoxidase]—meet in this common lumen, which connects with the terminal ramifications of the pancreatic duct." The process of trypsin formation, as I interpret it, thus involves the secretory functions of the spleen, in accord with the views of Schiff, Herzen, Pachon and Gachet and others. "Such a 'charging' of the pancreas by the spleen has been repeatedly suggested by Schiff," says Hammarsten,[15] "and his statements have not only been confirmed by these recent investigations but in part also explained." The more recent experiments of Levene and Stookey[16] afford additional evidence in the same direction.

The functional relationship between trypsin and the intestinal juices, *i.e.*, the succus entericus, includes a kindred process. An editorial writer[17] recalled the fact, referring to the succus entericus, that in the case of trypsin, "it had been found that the presence of a special body is necessary before the ferment is capable of exercising its activity." As to the nature of this agent, he says, "it has now been shown that this transformation is effected by a peculiar substance which has been termed *enterokinase* and which apparently belongs to a special class of cellular products which in themselves are inactive, but are *capable of activating certain ferments.* Of the mode of action and the chemical nature of enterokinase, we know practically nothing, and its origin even has not as yet been definitely ascertained."

Pawlow,[18] who introduced the term "enterokinase" nine years ago, refers to it in the following terms: "The succus entericus undoubtedly possesses the striking capability of augmenting the activity of the *pancreatic ferments*, and more especially the proteolytic. In the case of the latter, the increase often reaches to an astonishing degree. He who has once convinced himself of this by experiment will never doubt for a moment that this *accentuating* influence is *the most important function of the succus entericus.*" He also remarks: "The application of the usual tests for ferment action—namely, *destruction by boiling*, activity in very small quantities, and so on—convinced us [Schepowalnikow, his collaborator and himself] that in this case we were dealing in point of fact with a ferment. We had, therefore, discovered a ferment, not for this or that constituent of the food, but *a ferment of other ferments.*" *

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[14] Landois: *Ibid.*, p. 305.

[15] Hammarsten: "T. B. of Physiol. Chem.," fourth Amer. edition, p. 323, 1904.

[16] Levene and Stookey: Amer. Jour. of Physiol., vol. xii, p. 1, 1904.

[17] Editorial, Medical News, Dec. 31, 1904.

[18] Pawlow: "The Work of the Digestive Glands," Eng. edition, p. 159, 1902.

More recent work has only served to confirm Pawlow and Schepowalnikow's deductions. Thus, Bayliss and Starling[19] were led, by a study of the literature of the subject and comprehensive personal experiments, to conclude that while "trypsinogen is a stable body," . . . . "it is converted into trypsin by the action of enterokinase." They also state that "trypsin is not an expression for two bodies, enterokinase and trypsinogen acting together, but is a third substance produced as a result of the interaction of those two bodies, *i.e.*, *enterokinase* acts on trypsinogen *like a ferment* (Pawlow) *and converts it into trypsin.*" Finally they observe that enterokinase "has an extraordinary power of influencing the pancreatic juice" and that in one experiment 0.0001 cubic centimeter of an active enterokinase "was able to activate 5 cubic centimeters of pancreatic juice in three days."

That enterokinase, the identity and origin of which, we have seen, have remained unknown, contains *adrenoxidase* is shown in various ways. We have seen that while the activity of trypsin rapidly declines after 60° C.—which means that its zymogen, trypsinogen, is destroyed at that temperature—adrenoxidase is only destroyed when the boiling point is reached. Indeed, as observed by Moore and others, its active principle, that of the adrenals, requires several hours' boiling before yielding.

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* The italics of the last five words are Prof. Pawlow's.—S.

[19] Bayliss and Starling: Jour. of Physiol., vol. xxx, p. 61, 1903.

Now, enterokinase presents the same peculiarities. Not only, as stated by Pawlow, must the boiling point be reached for its destruction, but as observed by Biéry and Henri,[20] heating it twenty minutes to 120° C.—20 degrees above boiling—may not entirely destroy its action. We have seen also that all adrenal extractives are extremely sensitive to the action of alkalies. "The active trypsin," says Howell,[21] *i.e.*, the trypsinogen plus enterokinase, "is very easily destroyed, especially in alkaline solutions." That enterokinase is, like adrenoxidase, an oxidizing agent, is demonstrated by the experiments of Heidenhain, Sakharoff, and Barcroft and Starling.

Other facts point in the same direction. Schoenbein[22] over forty years ago showed that the blood and the various secretions of animals, as well as the juices of the many vegetable tissues studied, produced a blue coloration with guaiac in the presence of hydrogen peroxide. He ascribed this property to the presence of soluble ferments, trypsin, pepsin, etc. As stated by Oscar Loew,[23] however, "investigations of recent years have shown that the blue guaiac reaction is due to a separate enzyme belonging to a new group of *oxidases.*" In the light of the evidence adduced, the "oxidases" were obviously combined with soluble ferments referred to by Schoenbein. Finally, in the earlier editions (page 729), I concluded that "the oxidizing substance [now adrenoxidase] corresponds with Ehrlich's amboceptor." Benjamin Moore,[24] alluding to the investigations of Delezenne and Dastre and other French observers, says that they "regard the enterokinase as an 'amboceptor' in the language of Ehrlich, which serves to link together the attacked proteid and the trypsinogen, and so invokes the proteid cleavage."

Considered collectively, all these experimental facts indicate that *the substance termed by Pawlow "enterokinase" and also "a ferment of ferments" contains adrenoxidase.*

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[20] Biéry and Henri: cited by Benj. Moore, Hill's "Recent Advances in Physiol. and Bio-Chemistry," p. 110, 1906.

[21] Howell: "T. B. of Physiol.," p. 704, 1905.

[22] Schoenbein: *Loc. cit.*

[23] Oscar Loew: "Catalase," U. S. Dept. of Agriculture Rep., No. 68, 1901.

[24] Benjamin Moore: Hill's "Recent Advances in Physiol. and Bio-Chemistry," p. 109, 1906.

ADRENOXIDASE AS "SECRETIN;" ADRENOXIDASE PLUS NUCLEO-PROTEID AS ENTEROKINASE, AND THE ACTIVE PRINCIPLE OF ADRENOXIDASE AS THE FERMENT OF TRYPSIN.

As is well known, the activity of ferments is dependent upon the temperature to which they are exposed. "The digestive enzymes are very sensitive to changes in temperature," writes Moore,[25] "they all act most energetically at or slightly above the body temperature." The words "slightly above the body temperature" are very suggestive when it is recalled that fever and even hyperpyrexia mean a rise of but a few degrees above the normal temperature. Hammarsten[26] states, for example, that "many circumstances exert a marked influence on the rapidity of the trypsin digestion. With an increase in the quantity of enzyme present the digestion is hastened at least to a certain point, and the same is true also of an increase in temperature at least to about 40° C. [104° F.], at which temperature the proteid is *very rapidly* dissolved by the trypsin." He also says, referring to fibrin, the proteid generally used for such experiments: "Very considerable quantities of this proteid body are dissolved by a small amount of trypsin at 37° to 40° C. [98.6° to 104° F.]." When we recall that Metchnikoff found that it was a trypsin which destroyed bacteria in his phagocytic leucocytes, we cannot but admit that there is a striking coincidence between the febrile state and the temperature at which a germ-destroying ferment is very active. This suggests that we are dealing in this connection with an important feature of pathology.

How is the rise of temperature which enhances the efficiency of ferments brought about? In the first volume I ascribed this function to the interaction of the oxidizing substance (adrenoxidase) and another familiar blood-constituent, fibrinogen, a body whose only function is now thought to be concerned with coagulation of the blood.

Fibrin—the identical fibrin obtained by whipping blood—can, as we have seen, be split into two substances, fibrin-ferment and fibrinogen. That the former is the adrenoxidase was shown by the facts that it gave the blue coloration with guaiac (Arthus) and that this reaction only failed to occur when it had been heated to the boiling point, *i.e.*, 100° C. (Abelous and Biarnès). Fibrinogen, on the other hand, is, according to Schäfer, probably a loose combination of three substances, one of which alone is related to the question in point, *viz.*, nucleo-proteid, and termed such because it contains nuclein. Now, "the nucleins are *rich in phosphorus*," says Hammarsten,[27] "containing in the neighborhood of 5 per cent."

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[25] Moore: *Loc. cit.*, p. 320.
[26] Hammarsten: *Loc. cit.*, p. 328.

That fibrinogen and fibrin ferment (adrenoxidase) unite so readily to form the fibrin of shed blood betokens their mutual affinity. This fact is evidently of paramount importance in the vital process, for the nucleo-proteid constituent of fibrinogen is found as universally in plants and animals as is the oxidizing substance itself. Again, "the nucleo-proteids seem to be widely diffused in the animal body," says Hammarsten.[28] "They occur chiefly in the *cell-nuclei*, but they also often occur in the protoplasm." In a union between the *oxygen*-laden adrenoxidase and the *phosphorus*-laden nucleo-proteid we have a self-evident source of heat. Hence the fact that I ascribed (in the first volume) to a continuous reaction between the fibrinogen and the oxidizing substance (adrenoxidase) in the tissues and the blood-stream, not only the generation of heat in the animal organism, but also that of the heat energy to which ferments owe their exacerbations of activity. Thus a ferment is active in proportion as the relative quantity of fibrinogen and adrenoxidase present is great.

The activity of the reaction which occurs when phosphorus and oxygen are brought into contact under appropriate conditions hardly needs to be emphasized. "Ordinary phosphorus is very oxidizable," writes E. C. Hill,[29] "igniting spontaneously in air at 50° to 60° [C]. At lower temperatures it oxidizes more slowly with phosphorescence." Bunge[30] refers to oxygen in physiological functions as the "most potent source of energy."

The rôle of adrenoxidase is not only shown by the fact that as fibrin ferment it combines with the nucleo-proteid-laden fibrinogen as soon as blood is shed, but also in that this union can occur in the circulating plasma. This is well illustrated by the presence in the plasma of what have been termed blood-platelets (droplets of adrenoxidase, we have seen) *plus* nucleo-proteid. "According to the researches of Kossel and of Lilienfeld,"[31] says Hammarsten,[32] "the blood-plates consist of a chemical combination between proteid and *nuclein*, and hence they are called nuclein-plates by Lilienfeld, and are considered as derivatives of the cell nucleus." In view of the data I have adduced, they represent a combination of adrenoxidase and nuclein-laden fibrinogen, thus forming an exact counterpart, as to the bodies involved, of coagulation in shed blood. In fact, Hammarsten says in this connection, "It seems certain that the blood-plates stand in a certain relationship to the coagulation of blood." He also states[33] that "coagulation is retarded by cooling" and "by diminishing the oxygen"—additional features in which coagulation corresponds with fermentation.

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[27] Hammarsten: *Loc. cit.*, p. 125.
[28] Hammarsten: *Loc. cit.*, p. 56.
[29] E. C. Hill: "T. B. of Chemistry," Philadelphia, 1902.
[30] Bunge: *Loc. cit.*, p. 237.

The active part taken by adrenoxidase in the heat-producing process through its combination with the nucleo-proteid (shed by leucocytes as we shall see) in the blood, is illustrated by the influence of removal of the adrenals, the sources of its active principle, on temperature. That this is markedly lowered was first shown by Brown-Séquard. Schäfer, referring to the experiments of Marinesco, and Vassale and Sacchi, places "diminution of the body temperature" first among the results of bilateral extirpation. Hypothermia, as is well known, is a marked symptom of Addison's disease. Conversely, as previously stated, Oliver and Schäfer, Lépine, Morel and Reichert all observed that adrenal extracts caused a rise of temperature, "accompanied," in the case of the last named observer, "by increased metabolism." This points to the wide-spread character of the action of adrenoxidase, and to the presence in all parts of the body of the nucleo-proteid-laden fibrinogen with which it combines to liberate heat energy.

Indeed, as already stated, nucleo-proteid has been found in all parts of the organism and in enzyme-secreting elements or their products: *e.g.*, in gastric juice by Nencki and Sieber,[34] in the pancreas by Hammarsten,[35] in the liver by Halliburton,[36] in the muscles by Pekelharing,[37] in the heart-muscle by Bottazzi and Ducheschi,[38] in large quantities in the non-striated muscles by Munk and Velichi,[39] and in the brain by Levene,[40] etc. Hammarsten,[41] alluding to the presence of nucleo-proteid in the nervous system, says: "There does not seem to be any doubt that the proteids belong chiefly to the gray substance of the brain and to the axis-cylinders. The same remarks apply to the nuclein, which von Jaksch[42] found in large quantities in the gray substance."

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[31] Lilienfeld: Dubois-Reymond's Archiv f. Physiol, 1892 u. 1893.
[32] Hammarsten: *Loc. cit.*, p. 186.
[33] Hammarsten: *Loc. cit.*, p. 189.

In the intestines—as elsewhere in the body, as shown in the first volume—the nucleo-proteid is supplied by leucocytes and *is secreted by these cells as granulations.* Hardy and Wesbrook[43] state, as the result of personal experiments: "It appears to us to be clear that immigration of the oxyphile cells into the epithelium and thence into the lumen [of the intestine] is a process of constant occurrence, at times so slight as to be barely detectable, at other times so excessive that the epithelium appears to be riddled with these bodies. The most obvious change which the oxyphile cells manifest *within the epithelium* or the *lumen of the gut* is a diminution in the number of *oxyphile granules* even to the total disappearance of these structures." That the granules are *oxyphile* points to their identity as the phosphorus-laden nucleo-proteid granules (Sherrington, Milroy, and Malcolm[44]) which contribute to the formation of enterokinase by combining with adrenoxidase.

On the whole, the evidence available shows that *it is to an exacerbation of the heat liberated by a continuous reaction between the phosphorus-laden nucleo-proteid and the oxygen of the adrenoxidase that the augmentation of heat energy which endows ferments with increased activity should be ascribed.*

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[34] Nencki and Sieber: Zeitsch. f. physiol. Chemie, Bd. xxxii, S. 291, 1901.

[35] Hammarsten: *Ibid.*, Bd. xix, S. 19, 1894.

[36] Halliburton: Jour. of Physiol., vol. xiii, suppl., p. 806, 1892.

[37] Pekelharing: Zeit. f. Physiol. Chemie, Bd. xxii, S. 245, 1896.

[38] Bottazzi and Ducheschi: Il Morgagni, vol. xxxix, No. 10.

[39] Velichi: Centralbl. f. Physiol., Bd. xii, S. 351, 1898.

[40] Levene: Archives of Neurol. and Psycho-Path., vol. ii, Nos. 1 and 2, 3, 1899.

[41] Hammarsten: *Loc. cit.*, p. 406.

[42] von Jaksch: Pflüger's Archiv, Bd. xiii, S. 469, 1876.

[43] Hardy and Wesbrook: Jour. of Physiol., vol. xviii, p. 490, 1895.

[44] Sherrington, Milroy and Malcolm: Jour. of Physiol., vol. xxv, p. 105, 1899.

Returning to the intestinal pancreatic juice, we find it to possess, in keeping with all fluids endowed with fermentative properties, its nucleo-proteid. The latter was recently found by Stassano and Billon[45] to be *a constituent of enterokinase*. In other words, *enterokinase is a compound of adrenoxidase and nucleo-proteid.*

This leaves adrenoxidase unisolated. Another substance found in the intestinal secretions, however, meets all the chemical tests of the active principle of the adrenals, *i.e.*, that of adrenoxidase.

Bayliss and Starling[46] have given the name "secretin" to "a chemical substance which is formed in the mucous membrane of the upper parts of the small intestines under the influence of acid," meaning by the latter, of course, the hydrochloric acid derived from the stomach immediately above. This was confirmed by the observations of Pawlow, Popielski, Wertheimer and Lepage and others. Although Bayliss and Starling could not "give any definite suggestion as to the chemical nature of secretin," the tests they enumerate are clearly those of the adrenal active principle. Thus, while insoluble in absolute alcohol and ether, it becomes soluble when water is added to the former; the authors state that "a short boiling does not destroy it,"—a characteristic of adrenal extractives as shown by Moore. On evaporating a solution "the activity was found to disappear," a fact which they ascribe "to slow oxidation." The characteristic reducing power is shown by the fact that "the activity of a strong solution is very readily abolished by weak potassium permanganate." Adrenalin is not an alkaloid, according to Takamine, since, among other tests, it is not precipitated by tannin. Bayliss and Starling also say, alluding to secretin: "That it is not of the nature of an alkaloid or diamino-acid is shown by the fact of its not being precipitated by tannin." It dialyses through parchment paper, so do adrenal extractives. It promptly disappears when injected into the tissues —another peculiarity of adrenal extractives, readily accounted for when we consider that it soon becomes oxygen-laden and transformed into adrenoxidase.

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[45] Stassano and Billon: C. r. de la Soc. de biol., p. 623, 1902.

[46] Bayliss and Starling: Jour. of Physiol., vol. xxiv, p. 99, 1899; and vol. xxviii, p. 325, 1902.

Bayliss and Starling found, moreover, that secretin preparations made from the duodenum of the cat, rabbit, monkey and *man*, "were all active as regards the pancreatic secretion of the dog;" while on that of the rabbit and monkey they tested the secretin of the dog, rabbit, monkey and man, also with positive results. They concluded, therefore, that "the secretin of all these animals is one and the same body." These investigations have, as to their general features, been confirmed by Camus, Gley, Herzen and others. (Hammarsten.[47]) The conclusion of Bayliss and Starling that secretin is the specific chemical excitant of the pancreatic secretion is also sustained in the light of my views, since, as we have seen, it is adrenoxidase which endows trypsinogen with its activity in the pancreas.

On the whole, the following conclusions seem warranted: (1) *the composition of the pancreatic juice is as follows: the normal product of the pancreas, the zymogen or mother substance trypsinogen; adrenoxidase—a substance now known as "secretin;" and nucleo-proteid;* (2) *trypsin is formed when trypsinogen combines with enterokinase, a body composed of adrenoxidase and nucleo-proteid;* (3) *trypsin causes hydrolytic cleavage of proteids, and its proteolytic activity is due to the intrinsic heat-energy its oxygen-laden adrenoxidase and its phosphorus-laden nucleo-proteid liberate when combined.*

An additional conclusion warranted by the evidence submitted is that *trypsin owes its activity as a ferment to adrenoxidase, since it is the only one of its three constituents that is endowed with the properties of a ferment, i.e., of provoking catalysis.* The bearing of this fact becomes self-evident in view of Moore's[48] statement that "ferment actions are such catalytic reactions."

THE ACTIVE PRINCIPLE OF ADRENOXIDASE AS THE FERMENT OF PTYALIN, AMYLOPSIN, LIPASE, AND MALTASE, AND OF THE DIASTASE WHICH CONVERTS GLYCOGEN INTO SUGAR.

The fact that, as stated by Hammarsten,[49] the pancreatic juice (dog) contains "amylopsin, trypsin, steapsin and rennin," suggests that these ferments are all produced under similar conditions and that their zymogens owe their activity to adrenoxidase and nucleo-proteid. That such is actually the case, *i.e.*, that the process through which trypsin becomes a proteolytic ferment exemplifies that which prevails in the case of all pancreatic ferments, is sustained by considerable direct and indirect evidence.

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[47] Hammarsten: *Loc. cit.*, p. 322.
[48] Moore: Schäfer's "T. B. of Physiol.," vol. 1, p. 317, 1898.
[49] Hammarsten: *Loc. cit.*, p. 324.

The *starch-splitting ferment* of the saliva, ptyalin, is now considered by most authorities to be the same as that of the pancreas, amylopsin. As stated by Moore:[50] "In their behavior to change of temperature and reaction the two enzymes are identical; the rate of conversion of starch into other substances depends on the concentration of the enzymes in the solution"—a fact which plainly suggests that the differences observed can be "entirely produced by differences in concentration." The two ferments will, therefore, be considered together.

The first question to suggest itself is whether we are dealing with a ferment, since, as is well known, starch may be converted into sugar by ordinary chemical procedures.

That a ferment is the active agent in the physiological process is shown by the fact that Roberts[51] found that amylopsin could convert 40,000 times its weight of starch—obviously as the result of a fermentation. As the adrenal active principle of adrenoxidase is essentially a ferment—the *deus ex machina* of enterokinase—it meets the need in this particular. Again, we have seen that secretin strikingly corresponds as to its chemical reactions with the adrenal principle. Ptyalin, which is now considered identical with amylopsin, shows a similar correspondence with the same active principle, *i.e.*, adrenalin. It is precipitated by absolute alcohol, but as water is added to the latter its solubility increases; it acts best in a faintly acid solution. A pure ptyalin—which gave none of the proteid reactions—isolated by Cohnheim,[52] presented, moreover, the characteristic test of adrenalin: it resisted the boiling temperature. That the active ferment of ptyalin is that present in adrenoxidase is further shown by the fact that, as we have seen,

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[50] Moore: *Loc. cit.*, p. 328.
[51] Roberts: Lumleian Lectures, London, 1891.
[52] Cohnheim: Virchow's Archiv, Bd. xxviii, S. 241, 1863.

Schoenbein[53] produced a blue coloration of saliva and secretion of mucous membranes with tincture of guaiac in the presence of hydrogen peroxide.

As to the presence of nucleo-proteid in both amylopsin and ptyalin, the evidence is also direct. Not only have we seen that the pancreas is supplied with this body available for all its zymogens, including, therefore, amylopsin, but Hammarsten[54] includes among the constituents of saliva, both nuclein and nucleo-proteid.

All this is further sustained by the fact that the needs of the catalytic process which the presence of adrenoxidase entails are met by a very marked oxygen absorption, as shown in the following lines by Bunge:[55] "That oxygen passes through the capillary wall in the salivary glands is apparent, for the simple reason that the saliva contains free oxygen. So large an amount of oxygen passes out of the blood, therefore, that the cells of the glandular tissue cannot consume it, and the excess escapes into the secretion." What this illustrates, of course, is the marked vigor of the catalytic action sustained by the adrenoxidase. Again, Pflüger[56] ascertained the presence of absorbed oxygen in the submaxillary secretion with the aid of the gas-pump; he found that it amounted to from 0.4 to 0.6 per cent. of the volume of the saliva. This fact was confirmed by Hoppe-Seyler, who "found that the secretions of both the submaxillary and of the parotid contained oxygen."

That the starch-splitting ferment is, like trypsin, activated by adrenoxidase and nucleo-proteid, appears to me self-evident.

As to the *fat-splitting ferment* lipase (pialyn, steapsin), the data available are very scant. According to Moore,[57] "very little is known of the fat-splitting enzyme, pialyn, of the pancreatic juice. That the action is due to an enzyme, however, is shown by the following experimental observations: (*a*) The action is destroyed when the pancreatic juice or active pancreatic extracts are *boiled;* (*b*) it takes place in the presence of antiseptics, and hence cannot be due to bacteria"

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[53] Schoenbein: *Loc. cit.*
[54] Hammarsten: *Loc. cit.*, p. 286.
[55] Bunge: *Loc. cit.*, p. 246.
[56] Pflüger: Pflüger's Archiv, Bd. 1, S. 686, 1868.
[57] Moore: *Loc. cit.*, p. 339.
[58] Nencki: Arch. f. exp. Path. u. Pharm., Bd. xx, S. 367, 1886.

(Nencki[58]). That oxygen takes part in the process is suggested by the fact that, as stated by Landois,[59] its action on fatty acids is attended by the production of CO_2 and H in the absence of micro-organisms. Again, we have seen that Sakharoff found that ferments remained inactive in the absence of oxygen.

The rôle of the intestinal juice in the process is emphasized by the observations of Bunge,[60] that even after removal of the pancreas, the greater part of fat administered to dogs continued to be split into fatty acids and glycerin—a process which corresponds with that ascribed to enterokinase by Pawlow. The participation of the oxygen and nucleo-proteid of enterokinase in the cleavage of fat is also shown by the fact that, as stated by Moore,[61] the activity of lipase "is greatly increased by the presence of bile." Now, Glaessner[62] showed recently that this applied to diastatic ferments as well as to fat-splitting ferments—a fact which indicates that the latter must be activated by the same agents that activate ptyalin, amylopsin, etc. The identity of the agent which in bile produces this action is suggested by Moore's statement that "Paijkull[63] has proved that the mucin-like substance which gives bile its viscidity really belongs to the nucleo-proteids." As nucleo-proteid is necessarily secreted into the intestine, it plays in the fat-splitting process precisely the rôle it fulfills in conjunction with adrenoxidase in other fermentative processes reviewed. It is evidently, as in the case of trypsin, ptyalin and amylopsin, one of hydrolytic cleavage, for Claude Bernard[64] showed that the fat-molecule took up three molecules of water and split into glycerin and three molecules of fatty acid.

Although the evidence in the case of the fat-splitting ferment is partly inferential, owing to the paucity of experimental data, the temperature at which it is destroyed, its kinship to amylopsin and therefore ptyalin which colors guaiac blue; the facts that it is produced by the same organ as trypsin and that its activity is enhanced by contact with bile, a body rich in

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[59] Landois: *Loc. cit.*, p. 306.
[60] Bunge: *Loc. cit.*, p. 165.
[61] Moore: *Loc. cit.*, p. 239.
[62] Glaessner: Zeit. f. physiol. Chemie, Bd. xl, S. 465, 1904.
[63] Paijkull: *Ibid.*, Bd. xii, S. 196, 1888.
[64] Claude Bernard: Ann. de chim. et de phys., Sér. iii, p. 474, 1849.

nucleo-proteid, indicate that it differs in no way from trypsin as to the manner in which it is physiologically activated.

As stated by Landois,[65] "the pancreas also prepares a *sugar-splitting ferment*. If a solution of sugar is digested with an aqueous or glycerin extract of pancreas, the amount of sugar diminishes." This ferment is maltase, which converts maltose into dextrose, the sugar found in the urine in glycosuria. Maltase is also present in the saliva, which, we have seen, colors guaiac blue and contains nucleo-proteid. Wherever found, therefore, it is accompanied by adrenoxidase and nucleo-proteid, since these bodies are also present in pancreatic juice. Now, Cohnheim[66] was finally led, after a series of experimental investigations, to compare the formation of the pancreatic sugar-splitting ferment to that of trypsin as interpreted by Pawlow, *i.e.*, with enterokinase (which, we have seen, contains both adrenoxidase and nucleo-protéid) as the activating agent of the trypsinogen. A subsequent series of researches by the same investigator,[67] having for its purpose to identify the "glycolytic body" as he terms it, showed that it *withstood boiling*, and that it was soluble in water and *96 per cent.* alcohol. Both these tests are characteristic of the adrenal active principle, since, as we have seen, it is soluble in alcohol containing water, *i.e.*, 96 per cent. alcohol. Cohnheim mentions another test which applies to the adrenal principle, *viz.*, that it is insoluble in ether. Finally, as to the nature of the glycolytic body, he concludes that it is not a ferment—such as pepsin, trypsin, etc.—but a body closely allied as to its characteristics to the constituents of various internal secretions, among which he mentions *adrenalin* and *secretin*—the identical bodies which I have identified as the active principle of adrenoxidase as to the adrenalin, and as adrenoxidase as to secretin. Cohnheim was thus brought back to a conclusion which I had reached one year before him (see page 411 in the first volume), *viz.*, that "Lépine's glycolytic ferment is the oxidizing substance"—now the adrenoxidase.

In the light of the foregoing facts, however, the adrenoxidase is not itself the glycolytic agent, but it endows the latter, *i.e.*, the sugar-splitting ferment maltase, with its property as such, this ferment being composed of the pancreatic zymogen, adrenoxidase and nucleo-proteid. As such, it is an exact counterpart of trypsin, but acting on sugars instead of proteids.

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[65] Landois: *Loc. cit.*, p. 307.
[66] Cohnheim: Zeit. f. physiol. Chemie, Bd. xxxix, S. 336, 1903.
[67] Cohnheim: *Ibid.*, Bd. xlii, S. 401, 1904.

Closely allied to this process is that through which *glycogen* is converted into sugar. When, as shown by Minkowski, von Mering, Dominicis, von Noorden and others, the pancreas is removed from animals, glycosuria appears. This is due to the absorption into the blood of sugars ingested as such or derived from starches converted into sugar in the alimentary tract and eliminated by the urine. Thus Minkowski found, and his results were confirmed by Hédon,[68] that a fixed quantity of sugar, administered to animals deprived of their pancreas, caused an increase of sugar in the urine precisely equal to the quantity given. In normal animals, however, this morbid phenomenon does not occur. The several varieties of sugar and their anhydrides, dextrine and starches, contribute to the formation of glycogen, which is stored, as is well known, in the liver, to be, as first suggested by Claude Bernard, converted into sugar for use in the organism at large; the muscles in particular. Bernard concluded that this is effected by a diastatic ferment—a view which, according to Hammarsten, "is accepted by most investigators." I may recall in this connection that I pointed out in the earlier editions (page 404) the source of his ferment, *viz.*, the pancreas, the pancreatic juice reaching the liver by way of the splenic and portal veins, as an internal secretion. Indeed, J. Rose Bradford[69] states that "pancreatic diabetes may be produced not only by removal of the pancreas, but also by ligature of the pancreatic veins," a fact which indicates that obliteration of the vessels which carry, as interpreted from my standpoint, the pancreatic products to the splenic vein annuls the organ's functions as to its relations with the liver. This not only sustains Bernard's conception as to the intervention of a diastatic ferment, but it assimilates the latter to the ferment by which the conversion of starches into sugar is brought about in the intestine, *i.e.*, amylopsin and its homologue in the saliva, ptyalin, which we have seen contains both adrenoxidase and nucleoproteid.

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[68] Hédon: Archives de physiol., Jan., p. 154, 1893.
[69] J. Rose Bradford: Practitioner, Aug., 1900.

Diabetes—a form of this disease as least—should under these conditions be caused by an excessive production of amylopsin by the pancreas. Again, the overproduction of this ferment should be caused by an excess of adrenoxidase in the blood, since this body supplies the body at large with oxygen, and is the promotor of tissue metabolism. Briefly we should have (1) an increase of pancreatic activity entailing overproduction of amylopsinogen, (2) leucocytogenesis, which entails, as we will see, an increased production of nucleo-proteid, and (3) the active principle in adrenoxidase,—the three agents which jointly form the amylolytic or diastatic ferment to which the conversion of glycogen into sugar is due. That such is the case is shown by the fact that the injection of the adrenal principle into the blood, adding thereby to its normal content in adrenoxidase, gives rise to glycosuria.

We have seen, in the first volume, that Blum, Croftan, Herter and others caused glycosuria by injecting adrenal extractives. This has been confirmed by a number of investigators. Herter and Richards not only produced glycosuria in animals, whether the adrenal active principle was introduced endovenously, subcutaneously or endoperitoneally, but Metzger[70] found that when adrenal extract was given to dogs there was hyperglycæmia, *i.e.*, an actual increase of sugar in the blood. Finally, Herter and Wakeman[71] found, moreover, that compression of the adrenal glands, thus causing hypersecretion, caused glycosuria, and that removal of these organs or ligation of their vessels caused a "considerable fall of the sugar-content of the blood."

Considered collectively, all this evidence seems to me to show (1) *that the mode of formation of trypsin and the manner in which it is activated and endowed with its properties as a ferment, is common to all pancreatic ferments;* (2) *that all the pancreatic zymogens are converted into ferments by combining with adrenoxidase and nucleo-proteid;* (3) *that they are all activated by the joint action of adrenoxidase and nucleo-proteid;*

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[70] Metzger: Münch. med. Woch., Mar. 25, 1902.
[71] Herter and Wakeman: Amer. Jour. Med. Sci., Jan. 1903.

and (4) *that they all acquire their property as ferments from the active principle of the adrenoxidase they contain.*

THE ACTIVE PRINCIPLE OF ADRENOXIDASE AS THE FERMENT OF THE COAGULATION FERMENT, AND RENNIN AS "FIBRINOGEN PROPER." THE ZYMOGEN OF FIBRINOGEN PROPER.

A prominent gastric ferment is the familiar milk-curdling rennin or lab discovered by Hammarsten in 1872. The process of coagulation which rennin provokes in milk was regarded by this distinguished chemist as analogous to that of blood-coagulation, but he ascribed it to the specific ferment named. Analysis of the question in the light of my views suggests, however, that milk coagulation is an artificial process, *i.e.*, one which has no physiological application, and that it is caused incidentally when the ferment which causes blood coagulation is added to milk. This entails the conclusion also that such a ferment as "rennin" does not exist as a separate entity.

A curious feature of the milk-curdling ferment is that it is found in many plants, in the blood of invertebrates, and also in that of vertebrates which do not secrete milk. "The presence of rennin in the stomach of birds and fishes is very remarkable," says Moore,[72] "and points to some wider function at present unknown to us, since it cannot be supposed that in such animals the ferment plays any part in connection with the clotting of milk." Again, while rennin is found in the stomach, where it is supposed to carry on its function, a substance capable of producing similar effects also exists in other parts of the body. Thus, extracts of testes, liver, lung, kidney, muscle, spleen, thymus, thyroid, brain, small intestine, ovary and blood were all found by Edmunds[73] to induce the formation of casein when added to milk. Moreover, Moro and Hamburger[74] found that a drop of hydrocele fluid from an infant, to which a drop of human milk was added, clotted almost immediately.

Again, although thirty years have elapsed since rennin was discovered, the actual need or usefulness of a milk-curdling ferment in the stomach has not, as yet, been shown. Howell,[75] for instance, states that "the value of the curdling action is not at once apparent," but "we may *suppose*," he adds, "that casein is more easily digested by the proteolytic enzymes after it has been brought into a solid form." Bunge[76] says that "the significance of rennet ferment and casein coagulation in the stomach is still unexplained." Stewart[77] also says that "we have no precise knowledge" as to its exact function.

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[72] Moore: *Loc. cit.*, p. 334.
[73] Edmunds: Jour. of Physiol., vol. xix, p. 466, 1896.
[74] Moro and Hamburger: Wiener klin. Wochen., Jan. 30, 1902.
[75] Howell: "Amer. T. B. of Physiol.," vol. i, p. 296, 1900.

Conversely we have in the similarity between the blood and milk good ground for the belief that a phenomenon provoked in the former by a given ferment will likewise induce it in the latter. Harris[78] has called attention to the many points of resemblance between milk and blood coagulation. "Both fluids coagulate by an enzyme," says this investigator, "the clot entangling the solid bodies being jelly-like, filling the dish, then contracting and expressing serum and whey respectively. Decalcification of each prevents clotting. In both heat is given out during coagulation. In both a low temperature retards coagulation." He also states, however, that while "blood has all its factors for clotting within itself" . . . . "milk has not."

It is as a nutritional agent that milk differs from blood. This is shown by the relative structure of these fluids. "Milk is a perfect food, but blood is not," continues Harris; "blood-clot has fibers in a felt-work; curd has no visible fibers, but is molecular." Though derived from the blood, in other words, and containing its main components, the structure of milk *as it is provided by Nature,* is eminently fitted for the nutrition of the suckling.

The clot formed in shed milk by rennet becomes, therefore, an adventitious product, and the presence of "rennet" in plants, in the stomachs of animals which are not milk-fed, and in the blood of organs other than the stomach, suggests that we are dealing with a constituent of the general blood-stream irrespective of any specific action of milk.

The true identity of rennin is shown by the nature of the milk clot and its mode of formation.

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[76] Bunge: *Loc. cit.*, p. 109.
[77] Stewart: *Loc. cit.*, p. 304.
[78] Harris: Jour. Anat. and Physiol., vol. xxix, p. 188, 1895.

Referring to milk-curdling, Howell[79] says: "The whole process resembles the clotting of the blood not only in the superficial phenomena, but also in the character of the chemical changes." Granting that caseinogen, as its name implies, is a zymogen or mother substance and that it is an homologue of fibrinogen, we are brought to assimilate rennin to fibrin ferment. Yet, Moro and Hamburger have suggested, on the basis of their experiments, that milk might also contain fibrin ferment. Moreover, we have seen that the presence of oxidase —fibrin ferment—has been made evident by the guaiac test (Arthus), thus confirming Moro and Hamburger's surmise. If coagulation were ascribed to fibrin ferment, therefore, the process would have to be explained by an increase in the relative proportion of the latter in the milk—an obvious fallacy.

Fibrinogen, on the other hand, meets all the needs of the phenomena witnessed. It is not a normal constituent of milk, but a *sine qua non* of the blood coagulation. The fibrin ferment being present in milk, the addition of fibrinogen causes coagulation simply because it re-establishes conditions as they were in the blood-stream—conditions which *it is the function of the mammary glands to prevent.* This explains why "rennin" is found in the blood of some plants, fishes and birds, and in organs which should not contain it according to the prevailing doctrine, and why, also, fibrinogen, a constituent of the general blood-stream, can act as rennin.

Again, fibrinogen is no less able to provoke active fermentation than rennin. The fact observed by Hammarsten,[80] for instance, that one part of rennin can curdle 400,000 to 800,000 parts of milk, is but a parallel of the process evoked when trypsinogen and the nucleo-proteid-laden enterokinase combine to form the trypsin. The mere addition of a small amount of mother substance to a fluid containing ferment suffices to start this action, and the milk's adrenoxidase being the fibrin ferment, a small quantity of fibrinogen (plus calcium salts) suffices to start the process ascribed to rennin, *i.e.*, coagulation. And this process differs in no way from that ascribed to the latter: the caseinogen is split into two substances, the curd (casein) and a soluble proteid, by the fibrin ferment. The only difference in the clot is that, as already stated, it is not filamentous as is the fibrinous blood-clot.

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[79] Howell: "Amer. T. B. of Physiol," vol. I, p. 295, 1900.

[80] Hammarsten: Jahrb. u. d. Fort. d. Thier.-Chem., Bd. vii, S. 106, 1877.

This interpretation eliminates all the discrepancies which have attended rennin from the start and which have never been met.

Thus, we have seen that milk, as shown by Arnold, Spolverini, Marfan, Gillet, Wender and others, contains oxidase, *i.e.*, the fibrin ferment, but that it has not been found to contain fibrinogen. This suggests that the fluidity of the milk is a physiological necessity which the glandular elements of the mammary glands insure by preventing the access to it of this substance. Under these circumstances, it becomes evident that: (1) Rennin being fibrinogen, the addition of this body to milk causes clotting because adrenoxidase is present in the latter. (2) The clotting of human milk when hydrocele fluid is added to it (Moro and Hamburger) is due to the fact that the latter contains fibrinogen while the former contains fibrin ferment. (3) The clotting of milk by organic and blood extracts (Edmunds) is due to the fibrinogen combined with adrenoxidase which all such extracts contain. (4) The clotting of milk on adding pancreatic juice (Roberts, Edkins, Halliburton) is due to the presence in the latter of adrenoxidase and of the fibrinogen combined with it. (5) Rennin being fibrinogen, it is a normal constituent of the blood of invertebrates and of the fluids of plants.

On the whole, it seems evident that such a ferment as rennin, for which no specific function has so far been found, does not exist as a separate entity, and that, wherever it is associated with a given process, the rôle ascribed to it can be fulfilled by fibrinogen.

We must not, however, lose sight of the fact that fibrinogen contains several substances. Schäfer,[81] for instance, states that "fibrinogen is probably a mixture, or loose combination, of at least three substances: (1) *Fibrinogen proper*, coagulating at 56° C., (2) the globulin described by Hammarsten and termed *fibrino-globulin*, coagulating at 65° C., (3) a *nucleo-proteid*."

With which of these constituents does rennin correspond?

Rennin is evidently not adrenoxidase, which, we have now seen repeatedly, resists all temperatures up to 100° C., the boiling point, for Hammarsten states[82] that "if an active and strong infusion of the gastric mucosa in water containing 3 per mille hydrochloric acid is heated to 37–40° C. for 48 hours, the *rennin is destroyed,* while the pepsin remains." In neutral solution, however, rennin is only destroyed at 70° C.

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[81] Schäfer: *Loc. cit.*, vol. I, p. 165.

Is it fibrinogen proper?

While fibrin is formed, as is well known, when blood is withdrawn from the vessels, Alex. Schmidt observed that pericardial, ascitic and other fluids did not coagulate spontaneously notwithstanding the presence of fibrinogen in them, but that they did so on the addition of blood-plasma. He attributed this result to a combination of the serum-globulin and fibrin ferment. Hammarsten[83] showed, however, that serum-globulin played no rôle in fibrin formation, and that by half saturating blood-plasma with sodium chloride, a precipitate was obtained, "fibrinogen proper," which by the action of Schmidt's fibrin ferment was converted into fibrin. Fibrin ferment being, as we have seen, adrenoxidase, the formation of fibrin suggests itself as another example of the influence of the adrenoxidase on a zymogen. It becomes a question, therefore, whether fibrinogen proper actually plays the same rôle here that trypsinogen does in the building up of trypsin.

If such is the case, the third constituent of the triad we have met in all ferments so far studied should also be present, *i.e.,* nucleo-proteid. That it is present is strikingly shown by the following quotation: "Fluids which collect in the serous cavities of the body (pericardial fluid, hydrocele fluid, ascitic fluid) frequently contain no leucocytes," writes Schäfer.[84] "When this is the case, they are also *devoid of nucleo-proteid and of the property of spontaneous coagulation, although they contain fibrinogen.*" It is evident, therefore, that coagulation cannot occur without nucleo-proteid. Indeed, coagulation occurs whether this body be derived from the blood or from the cellular elements. Buchanan[85] found that extracts of lymphatic glands and various tissues caused coagulation. "But it is only quite recently," says Schäfer, "that the active substance extracted by Buchanan has been examined and found to belong to the class of bodies known as nucleo-proteids." From this standpoint, therefore, fibrinogen proper (rennin) asserts itself as a zymogen.

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[82] Hammarsten: *Loc. cit.,* p. 305.
[83] Hammarsten: Arch. f. d. ges. Physiol., Bd. xix, S. 563, 1879.
[84] Schäfer: *Loc. cit.,* vol. i, p. 165.
[85] Buchanan: cited by Schäfer: "T. B. of Physiol.," vol. i, p. 168, 1898.

This is shown, moreover, by the chemical connection between nucleo-proteid and fibrinogen proper. These two bodies are closely linked in their solutions and may be precipitated by the same agents. "The nucleo-proteid is precipitated from oxalate plasma by allowing it to stand for twenty-four hours at 0° C.", writes Schäfer. "The addition of acetic acid also throws it down but not in its pure form, for *fibrinogen is carried along down with it.*" This represents undoubtedly the compound met with in all the reactions previously considered, for the same author says, "Fibrin obtained by whipping blood leaves a considerable *phosphorus-containing residue* (*nuclein*) after subjection to peptic digestion."

Rennin, as studied from various standpoints, thus asserts itself as a zymogen *fibrinogen proper,* which becomes active when *nucleo-proteid* and *fibrin-ferment* (adrenoxidase) are present—all constituents of the blood. Hence its behavior precisely as if it were a *bona fide* enzyme such as trypsin—in the light of prevailing views. That no satisfactory function has been found for it in the stomach is also explained: the zymogen itself, *i.e.*, the fibrinogen proper, is not a usual constituent of the gastric juice, although both nucleo-proteid and, as we will see, fibrin ferment are. Indeed, this becomes evident when we take into account the mode of preparation of "rennin," viz., by infusion either of the stomach or of its mucosa, or, in other words, of *tissues* rich in blood and leucocytes, and therefore rich in fibrinogen, including its zymogen, fibrinogen proper. This does not invalidate the fact that gastric juice itself may provoke coagulation, since it contains nucleo-proteid while fibrinogen proper and fibrin ferment are ubiquitous constituents of blood from which its fluids are derived. What it does show, however, is that *the gastric juice does not include as a functional entity an autonomous ferment such as "rennin," which has no existence as such.*

Direct experimental evidence to the latter effect was recently contributed by Pawlow and Parastschuk[56] which led to the conclusion, previously formulated by Danilewsky, that the coagulation of milk is, from the standpoint of the experimenter, an *accidental* expression of a *general* reaction, and that a separate and individual milk-curdling ferment does not exist. They fail, however, to show the *cause* of the coagulation, attributing it theoretically with Danilewsky to some constituent developed during the digestion of proteids by pepsin and forming part of the latter.

My own view that *the coagulation of milk attributed to rennin is in reality due to the ferment which causes coagulation of the blood, and that "rennin" is one of the constituents of this ferment, i.e., fibrinogen proper, a zymogen*, is not only sustained, we have seen by considerable direct and indirect evidence, but the active agent it introduces is one which logically meets the needs of the process.

All this has also served to show (1) *that the zymogen of coagulation is fibrinogen proper:* (2) *that like all other ferments, the coagulating ferment is composed of this zymogen, nucleo-proteid and adrenoxidase:* (3) *that fibrinogen proper not being itself a ferment, it is activated, like the pancreatic zymogens, by the adrenal ferment in the adrenoxidase with which it is combined;* and (4) *that the coagulating ferment acquires its properties as such from the adrenal ferment of the adrenoxidase it contains.*

THE ACTIVE PRINCIPLE OF ADRENOXIDASE AS THE FERMENT OF PEPSIN.

The presence of adrenoxidase and nucleo-proteid in the gastric juice and in pepsin is shown by direct and indirect evidence.

As to adrenoxidase, Schoenbein[57] found that the *gastric juice* gives a blue coloration with guaiac. We have seen, in the case of other ferments, that fermentation in which oxidases took part was attended by an output of CO_2. Bunge[58] states that "the gases which are formed by the process of fermentation in the stomach are *carbonic acid gas*, hydrogen, and marsh gas."

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[56] Pawlow and Parastschuk: Zeit. f. physiol. Chemie, Bd. xlii, S. 415, 1904.
[57] Schoenbein: *Loc. cit.*
[58] Bunge: *Loc. cit.*, p. 142.

He also refers to a case of dilatation of the stomach studied by Kuhn[89] in which "one liter of gastric contents developed four liters of gas in four hours when kept outside of the body at the body temperature." This gas was found to contain twenty per cent. of carbon dioxide.

The presence of nucleo-proteid is as evident. Thus Nencki and Sieber[90] found nucleo-proteid in the gastric juice. Moore, moreover, states that while in pure gastric juice the acidity is due chiefly to hydrochloric acid, it is also due "in part, to acid phosphates and phosphoric acid."

. The following lines of Hammarsten[91] are striking in this connection, when we consider that the presence of such a substance as adrenoxidase was not suspected by the author: "As chief organic constituent, perfectly fresh gastric juice (of dogs) contains a very complex substance (or perhaps a mixture of substances) which coagulates on *boiling* and which separates on strongly cooling the juice. This substance is considered by certain experimenters (Nencki and Sieber, and Pawlow) as the conveyer of the several *ferment actions* of the gastric juice, *i.e.*, the pepsin as well as the rennin action." By "conveyor" is meant "transmitter," the characteristic property of the adrenoxidase acting as a catalytic in relation to ferments in general, its identity as such being further shown by its coagulation temperature, the boiling point. With Schoenbein's observation that the gastric juice gave the blue coloration to guaiac, the evidence that the gastric juice contains what might be termed "gastrokinase" as a counterpart of Pawlow's enterokinase, may be considered as conclusive. Its purpose is evidently the same as the latter, since, as stated by Landois,[92] "the glands themselves contain no pepsin but only a zymogen," *i.e.*, pepsinogen.

The composition of *pepsin* also coincides with that of trypsin. As to the pepsinogen, Edkins[93] states that "though the chief cells will yield pepsin, yet they do not actually contain pepsin. If the granules then are connected with pepsin, it must be in some antecedent form. The probable explanation of this is that the granules of the chief cells consist wholly or in part of *pepsinogen*, the precursor of pepsin." Hammarsten[94] regards as "proved" the statement of Schiff[95] that there exists "a substance forming pepsin, a pepsinogen or propepsin."

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[89] Kuhn: Zeit. f. klin. Med., Bd. xxi, S. 584, 1892.
[90] Nencki and Sieber: Zeit. f. physiol. Chemie, Bd. xxxii, S. 291, 1901.
[91] Hammarsten: *Loc. cit.*, p. 298.
[92] Landois: *Loc. cit.*, p. 293.
[93] Edkins: Schäfer's "T. B. of Physiol.," vol. i, p. 533, 1898.

The presence of the adrenoxidase is evident. We have already seen that Nencki and Sieber, and Pawlow, have ascribed to what they consider the chief organic constituent of fresh gastric juice, the function of a "transmitter" or catalytic, pepsin being mentioned as one of the bodies influenced. This catalytic body was said to be destroyed when boiled, thus indicating its identity as the active principle of an oxidase, *i.e.*, adrenoxidase. That the latter is intimately connected with pepsin is also shown by the fact that it meets the tests which indicate the presence of its active principle, *i.e.*, that of the adrenal secretion. Thus, Glaessner[96] found in the pyloric end of the stomach what he termed "pseudopepsin," which in turn yielded tryptophan (Neumeister). This substance is even now of unknown composition, though found in the pancreatic juice nearly a century ago by Tiedemann and Gmelin.[97] When compared with the characteristic tests of adrenal extract the correspondence is suggestive: both tryptophan and adrenalin become rose-red on the addition of chlorine water; they both react in the same manner to a bromine solution. Both are but slightly soluble in ordinary alcohol. Again, Hammarsten[98] states that pepsin "is as difficult to isolate in a pure condition as other enzymes." This accounts for the fact that all the soluble ferments, including pepsin, were found by Schoenbein, Flügge, Epstein, Jacobson and others to decompose hydrogen peroxide, and by Schoenbein and others to give the guaiac blue reaction—additional proof that the contaminating substance is adrenoxidase.

As to the nucleo-proteid, Hammarsten[99] states that while an extra-pure pepsin, *i.e.*, that of Pekelharing, "was free from phosphorus and yielded no nucleo-proteid," thus pointing to the latter as a possible contaminating body, "pepsin, according to

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[94] Hammarsten: *Loc. cit.*, p. 307.

[95] Schiff: "Leçons sur la physiol. de la digestion," Florence, 1867.

[96] Glaessner: Hofmeister's Beiträge z. Chem. u. Physiol. u. Path., Bd. I, 1901-02.

[97] Tiedemann and Gmelin: "Recherches expér. physiol. et chim. sur la digestion, etc.," 1827.

[98] Hammarsten: *Loc. cit.*, p. 299.

[99] Hammarsten: *Loc. cit.*, p. 300.

Nencki and Sieber, was rich in phosphorus and contained nucleo-proteid."

In the presence of all these tests—those pertaining to pepsin confirming the data afforded by those upon the gastric juice —it is difficult to escape the conclusion that pepsin is built up in the same manner as trypsin, pepsinogen replacing trypsinogen, and that it owes its ferment to its adrenoxidase. We may conclude therefore, (1) ***that the gastric zymogen, pepsinogen, is converted into pepsin by combining with adrenoxidase and nucleo-proteid;*** **(2)** ***that pepsinogen is activated by the joint action of adrenoxidase and nucleo-proteid; and*** **(3)** ***that pepsin acquires its property as a ferment from the adrenal ferment of the adrenoxidase it contains.***

THE ADRENAL ACTIVE PRINCIPLE AS THE FERMENT OF FERMENTS; AND ALL HYDROLYTIC FERMENTS AS COMPOUND BODIES CONTAINING A ZYMOGEN, NUCLEO-PROTEID AND ADRENOXIDASE.

Having ascertained the general composition of the various hydrolytic ferments, it becomes a question whether the conclusions reached are in accord with what data the direct analyses of these ferments have furnished. That they harmonise is shown in the following pages.

B. Moore,[100] in an analytical review, says: "Little is known regarding the chemical nature of enzymes, because all attempts to isolate them in a state of purity have hitherto failed. In fact," adds the author, "there is nothing to give certainty that at the end of any process the product in the case of such complicated substances is pure." Still, he also states that "in elementary composition the enzymes do, however, resemble the proteids more than any other class of bodies." As this statement applies to hydrolytic ferments in general, we may infer that all these ferments contain proteids—in accord with the direct evidence I have submitted in the present chapter. Again, Moore refers only to simple proteids while those we found in the various ferments were invariably the phosphorus-laden nucleo-proteid. Later studies have shown that the proteids bound up with ferments contain phosphorus. "Macallum has shown microchemically," says an editorial writer,[101] "that phosphorus is closely associated with the formation of zymogen granules in cells, which seem to be started in the nucleus, and there are many other observations suggesting that certain ferments are closely related to the nucleo-proteids. This is particularly true of the oxidases." We may conclude, therefore, in view of the presence of nucleo-proteid in all the ferments studied in this chapter, that the proteids present in the ferments in general, as implied by Moore, are nucleo-proteids.

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[100] B. Moore: Hill's "Recent Advances in Physiol. and Bio-Chem.," p. 117, 1906.

The presence of zymogens in hydrolytic ferments needs hardly to be emphasized. After referring to the fact that Langley discovered pepsinogen and Heidenhain trypsinogen, Moore says, that "since then, the existence of a pro-ferment [zymogen] has been shown for most of the enzymes." This applies to all the ferments we have reviewed.

The presence of the third constituent, adrenoxidase, may be shown by tracing to its source the characteristic property of ferments, catalysis. Here, again, as we have seen, Moore[102] speaks of ferment actions as being "such catalytic reactions," thus characterizing catalysis as a property of all ferments. To which of the three constituents can we attribute this property?

That the nucleo-proteid need not be considered as a possible factor in this connection is obvious. Neither does the zymogen possess fermentative activity. Thus, Moore writes: "These zymogens, as has been stated, are inactive while in the cell and exist in granular form visible under the microscope; they are converted into the active form, either at the time of secretion or later, on coming in contact with certain substances which have been termed zymo-excitators, or, in certain cases, kinases." He then refers to Pawlow's enterokinase as an example of these agents, and to the belief of this investigator that this body is a "ferment of ferments." It is to enterokinase, therefore, that we are relegated for the agent which confers the properties of a ferment upon the zymogen.

To the questions: what is the agent *in* enterokinase which endows trypsinogen with the properties of a ferment, and what is the source of this agent, however, no answer is vouchsafed. These features of the problem do not seem to have, so far, engaged the attention of investigators. Indeed, though Delezenne, Camus and Gley and others were led experimentally to agree with Pawlow as to the effects witnessed, some contend that they are not due to a ferment. A suggestive fact asserts itself in this connection, however, *viz.*, that the main objections that have been raised are annulled when, in accord with my own view, adrenoxidase is considered as one of the constituents of the "ferment of ferments." Thus Delezenne and Dastre[103] deny that it is a ferment, but regard it "as an 'amboceptor,' in the language of Ehrlich, which serves to link together the attacked proteid and the trypsinogen and so invokes the proteid cleavage." Now, we have seen that adrenoxidase *is* Ehrlich's amboceptor and that it becomes linked with trypsinogen to cleave the proteid. If we asked Delezenne and Dastre to point to the constituent of the "amboceptor" which brings about such a result, their answer could only be that of Ehrlich, *i.e.*, that the nature of this body is unknown. "Proteid cleavage" whenever witnessed in the organism is due to hydrolysis provoked by a ferment; can they assert that we have here an exception to this rule? Not without introducing suppositious postulates—a weak weapon to offset the mass of evidence I have adduced in this and the preceding chapter as to the presence of the adrenal active principle in enterokinase. Largnier des Barcels, Biéry and Henri[104] have also pointed out as evidence against enterokinase being an enzyme, that it is "much more slowly destroyed by heat than are most enzymes," all having found that it could resist boiling, and in some instances higher temperatures. We have seen that of all the ferments, that containing the adrenal principle is the only one which remains unaffected by heat up to the boiling point and that it can even resist the latter several hours.

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[101] Editorial, Jour. Amer. Med. Assoc., Feb. 17, 1906.
[102] Moore: Schäfer's "T. B. of Physiol.," vol. i, p. 317, 1898.

That we are dealing with a ferment is emphasized, moreover, by direct experimental testimony. "Bayliss and Starling," writes Moore, "have brought forward strong evidence in favor of enterokinase being a ferment. Thus, they have shown that there is no stoichiometric relationship between the amount of trypsinogen and the amount of enterokinase necessary to activate it, as little as 0.0001 cubic centimeter of an active enterokinase being capable of activating 5 cubic centimeters of pancreatic juice provided it was allowed two or three days to act." This sustains the evidence adduced to the effect that enterokinase is activated by a ferment—that to which secretin owes its activity and the chemical properties of which are precisely those of the active principle of the adrenal secretion. The conclusion is warranted, therefore, that *enterokinase contains a ferment and that it owes its property as a "ferment of other ferments" (Pawlow) to the active principle which its adrenoxidase contains, i.e., that of the adrenal secretion.*

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[103] Delezenne and Dastre: cited by Moore: Hill's "Recent Advances in Physiol. and Bio-Chemistry," p. 109, 1906.

[104] Biéry and Henri: *Ibid.*

Such being the case, we are brought, by the evidence submitted in this and the previous chapter, to consider the adrenal active principle as the sole ferment of ferments. Not only have we seen that the character of a ferment is determined by its zymogen, but we found that in every instance it was the adrenal principle of its adrenoxidase which endowed the ferment molecule, so to say, with the characteristic of a ferment.

The ability of the adrenal principle to carry on such a process is, in the light of available evidence, beyond question. Moore,[103] we have seen, states that ferments are catalytic agents, adding, however: "But when we say that ferments act catalytically, the problem of how they act is by no means solved; we have merely found a name for it." Now, Loew[104] was led to conclude in the course of an extensive research that "there does not exist a group of organs or any organ, or even a single vegetable or animal cell that does not contain some catalase,"—a conclusion sustained by the testimony of Bertrand, Abelous and Biarnès, Phisalix, Schmiedeberg, Jaquet, Salkowski and other investigators, who found that the oxidases in all plants, invertebrates and vertebrates studied by them acted as catalytics.

A salient feature of the problem left in abeyance so far requires elucidation at this time, *viz.*, the independence of the catalytic action from the oxidizing action of oxidases observed by many investigators, and which led Jolles[107] to conclude that the blood contained both oxidases and catalase. The reason for this becomes plain—in the light of my views—when it is borne in mind that while the *adrenoxidase* as such is the oxidizing body, its *active principle, i.e.,* the adrenal active principle, is the catalytic. The two separate functions are thus fulfilled by the adrenoxidase, its active principle, embodied in the adrenal secretion, enabling the latter to take up the oxygen in the air of the pulmonary alveoli to transfer it via the red corpuscles and the blood-plasma to the tissues. It is strictly as an "oxygen transmitter" (using Traube's phrase) therefore, that the active principle of the adrenals behaves in the process, *i.e.,* as a pure catalytic.

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[103] Moore: Schäfer's "T. B. of Physiol.," vol. I, p. 317, 1898.
[104] Loew: *Loc. cit.*

Finally, Poehl[108] wrote recently, referring to the adrenal principle: "This body brings about reduction processes when present in such very small quantities that I cannot otherwise than see in adrenal (*sic*) a specifically positive katalysator of such processes. If we observe these reactions, we must conclude that we have here no ordinary reagent, that is to say, not a chemical body which enters into a change in which it is consumed itself, but on the contrary, that adrenal is a real katalysator which undergoes no change." Applying this concept to the human adrenals, the strength of my position will become apparent. Indeed, Jolles has not only ascertained, as previously stated, that the human blood is endowed with oxidizing and catalytic properties, but he observed that these properties bear a definite relation to the number of red corpuscles present, being raised in proportion as their number is increased. As I have shown that these corpuscles are storage-cells for adrenoxidase—the albuminous oxyhæmoglobin—the cause of this relationship is self-evident, provided, however, the active principle of the latter—that of the adrenals—is considered as a catalytic.

From all directions, therefore, the evidence available leads to the general conclusion *that the active principle of the adrenal secretion is the only true ferment in the organism, and that all bodies now known as hydrolytic ferments owe their activity as*

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[107] Jolles: Münch. med. Woch., Nov. 22, 1904.
[108] Poehl: Indian Lancet, May 23, 1904.

such to the adrenal active principle which one of their constituents, adrenoxidase, contains.

As corollaries to this fact, additional conclusions, based on the evidence recorded in the present chapter, are now in order:

(1) *That adrenoxidase fulfills two functions simultaneously: (a) that of catalytic, carried on by the active principle of the adrenal secretion it contains, and (b) that of oxidizing substance, after the adrenal secretion has become oxygenized in the lungs, and converted into adrenoxidase.*

(2) *That hydrolytic ferments are composed of three substances: (a) a zymogen, which endows the ferment with its specific character; (b) adrenoxidase, which confers upon the zymogen its properties as a ferment and catalytic; and (c) nucleoproteid, the phosphorus of which by combining with the oxygen of the adrenoxidase liberates heat energy and thus governs the activity of the ferment.*

CONCLUDING REMARKS.—Since Schwann, in 1836, demonstrated the presence of pepsin in the gastric juice, many theories have been introduced to account for the process of fermentation. "The general point of view regarding the mode of action of enzymes that is most frequently met with to-day," wrote Howell in his text-book,[109] "is that advocated especially by Ostwald. He assumes, reviving the older view (Berzelius), that the ferment actions are similar to those of catalysis." We have seen, however, that, as stated by Moore, this affords only a name for the process. The identity of the catalytic agent, its origin in the body and the manner in which it influences the substances with which it is linked have remained unknown. These three cardinal features are pointed out in the foregoing pages.

Moore[110] has likewise expressed the view that "little is known regarding the chemical nature of enzymes, because all attempts to isolate them in a state of purity have hitherto failed." The data submitted in these pages also indicate why laboratory methods have remained sterile in this connection, *viz.*, that the bodies which have been regarded as ferments (or enzymes) are in reality not ferments at all, but compounds of several substances having marked affinity for one another, and formed adventitiously when removed from their normal environment, the living body. As will be shown in the next chapter, one of these substances, *proteid, is a passive constituent of these so-called ferments*, while the three others, the zymogen, the nuclein and the adrenoxidase, are active, the active principle of adrenoxidase remaining, as stated above, the only true ferment.

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[109] Howell: "T. B. of Physiol.," p. 658, 1905.
[110] Moore: Hill's "Recent Advances in Physiol.," &c., p. 117, 1906.

THE TRIADS.—The compounds now termed "ferments" represent, nevertheless, aggregates of bodies which jointly take part in all fermentative processes, and it is necessary, in order to interpret satisfactorily the functions in which they take part, to treat them as autonomous entities. Especially is this desirable in view of the fact that as such they retain the specific properties now attributed to them as "ferments." In succeeding chapters, however, they will not be referred to as ferments, but as "triads," each being composed of a zymogen, nuclein and adrenoxidase. To indicate the specific action of each triad, the familiar terms "proteolytic," "amylolytic," "lipolytic" and "glycolytic" will be employed as qualifying adjectives, according to whether the food-stuff hydrolyzed is proteid, starch, fat or sugar. Thus the triad which acts on proteids will be referred to as the "proteolytic triad;" that acting on sugars as the "glycolytic triad," etc.

CHAPTER XV.

THE ADRENAL ACTIVE PRINCIPLE AS THE DYNAMIC ELEMENT OF LIFE AND THE GRANULATIONS OF LEUCOCYTES AS THE LIVING SUBSTANCE.

THE LEUCOCYTES AS TISSUE BUILDERS.

Beddard, referring to the end-products of intestinal digestion in Leonard Hill's recently published (1906) treatise, writes:[1] "Our knowledge of the actual path taken by different substances is extremely meagre. We know that the products of fat digestion pass into the epithelial cells, but we know nothing of the path taken by the products of proteid and carbohydrate digestion."

In the first volume[2] I pointed out that the granulations of the leucocytes played a far more important rôle in physiological functions than was credited to them in text-books, and that in all tissues these granulations were a source of energy when brought into contact with the oxidizing substance, *i.e.*, adrenoxidase. The final conclusion submitted, after showing that the leucocytes took up the products of intestinal digestion in the alimentary canal to convert them into granulations which they deposited in the tissues, was that these cells supplied "the entire organism with the agencies which combine with the oxidizing substance to insure the continuation of life and the efficiency of all organic functions." Additional researches have only served to strengthen this conclusion.

A bar to progress in our knowledge of the function of these minute bodies is the prevailing view that "elementary granules [the granulations of leucocytes] are minute particles of proteid matter, probably arising from the *disintegration* of white corpuscles or of the blood-platelets." That leucocytes do not physiologically yield their contents by becoming decomposed or ruptured in the intestinal cavity or in the blood, has been repeatedly emphasized. Dastre,[3] after a careful review of the labors of other investigators and personal experiments, lays stress upon "the erroneous character of the classic doctrine," having found, in accord with the views of Buchner, that leucocytes were not the fragile cells they were generally believed to be. Microscopical observations showed that, as previously observed by Hayem, Ranvier and Stassano, coagulation of blood, to which these cells are known to contribute, occurred without any destruction of leucocytes, a process thought necessary, according to the prevailing doctrine, for the escape of the cell contents. Such being the case, he was led to ascribe the elimination of fibrin-ferment by these cells to osmosis. Arthus[4] ascertained experimentally, however, that they actively *secreted* this ferment. "In the protection of the organism against hæmorrhages," says this observer, "leucocytes play a secretory, active, physiological, rôle. They are not the passive agents which, as has been erroneously supposed, generate fibrin-ferment by cadaveric destruction." Indeed, I suggested in the first volume[5] that the networks in these cells are canaliculi which traverse them in all directions, and that their digestive vacuole, their nucleus, and their canalicular system (the mitoma), point to them as highly-organized, though diminutive, secreting organs. "The various ferments they contain," says Carles, in a recent work,[6] "make of each cell a minute laboratory."

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[1] Beddard: Hill's "Recent Advances in Physiology and Bio-Chemistry," p. 643, 1906.

[2] *Cf.* vol. I, pp. 677 to 728 in the first three editions.

Considerable evidence to the effect that leucocytes are secretory organs is afforded by the researches upon the identity and functions of the leucocytic granules, which Hankin, fourteen years ago, was first to regard as secretory products. As we have seen,[7] Kanthack, Hardy and Keng have taken much the same view. No less an authority on the subject than Ehrlich also considers granulations in the light of a secretion, and holds that certain basophile granules constitute a preliminary step (*Vorstufe*) in the elaboration of typical eosinophile granulations. That they are developed with relative suddenness from non-granular mononuclears, and that they are constantly being developed, also suggests, according to Levaditi,[8] that they are secretory products. Stokes and Wegefarth[9] observed, in blood taken from some 500 patients, that at 35° C. the leucocytes became actively amœboid, their rapid motions resembling the swarming of bees around a bee-hive, and that after this the number of free granules in the plasma was increased. Sangree[10] saw eosinophile granulations leave the cell and wander away oscillating very actively. Bail[11] also saw granulations leave the periphery of the cell. Gulland[12] noted that leucocytes show a marked tendency to leave their granules behind them. Finally, Leo Loeb[13] observed that if a cell was drawn out with a needle, in order to produce the elimination of a widely diffused mass of granules, many granules could be "seen to move very actively."

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[3] Dastre: C.-r. de la Soc. de Biol., vol. lv, Nov. 14, 1903.

[4] Arthus: *Ibid.*

[5] *Cf.* vol. i, pp. 677 to 728, in the first three editions.

[6] Carles: "Du rôle des leucocytes dans l'absorption et l'élimination," Paris, 1904.

[7] *Cf.* vol. i, p. 679 *et seq.*, in the first three editions.

What is the origin of these granulations? Are we dealing with a *sui generis* product of the leucocytic protoplasm, or with the end-products of materials ingested by the cell? If, as shown above, we have abundant proof that leucocytes secrete their granules, we have in phagocytosis as evident a demonstration that they ingest assimilable materials; and if to this we add the known facts that they contain proteolytic ferments, and that they are able to digest what they ingest, we cannot but conclude that their granulations are elaborated out of the materials they appropriate while carrying on their function as scavengers.

This, in turn, suggests another question: May the food-materials of the alimentary canal not serve as their main source of supply for this purpose? Not only do the leucocytes ingest food-stuffs in the intestinal canal, as shown below, but also the "ferments," *i.e.*, the various hydrolytic triads which carry on the digestive process in the intestine, to continue this process in their digestive vacuole and elaborate granulations as end-products.

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[8] Levaditi: "Le leucocyte et ses granulations." Paris, 1902.
[9] Stokes and Wegefarth: Bull. Johns Hopkins Hosp., Dec., 1897.
[10] Sangree: Phila. Med. Jour., Mar. 12, 1898.
[11] Ball: Berl. klin. Woch., Oct. 11, S. 887, 1897.
[12] Gulland: Jour. of Physiol., vol. xix, p 385, 1896.
[13] Leo Loeb: Univ. of Penna. Med. Bull., Apr., 1905.

According to present teachings, the products of intestinal digestion pass into the general circulation in liquid form. Moore,[14] for instance, says: "The new materials formed by the action of the *intestinal epithelial cells* on the absorbed products of digestion pass out of these cells into the lymphoid tissue of the villus underlying them. The modified carbohydrates and proteids pass in solution into the lymph which bathes the tissue, and in *soluble form* are absorbed by the capillary vessels of the villus, thus passing directly into the portal circulation, while the fats leave the epithelial cells as fat globules, and are carried as such past the capillary network of the villus, to enter the lacteal situated in the axis of the villus." Yet, as stated by other physiologists, Brubaker,[15] for example, "the mechanism by which the [epithelial] cells effect this passage of the food is but imperfectly understood." Indeed, in a recent monograph L. Mendel,[16] reviewing the advances in our knowledge of the chemical processes of digestion, remarked that "beyond the intestinal wall, in the blood and lymph stream, the cleavage products seem, for the most part, to be *missing*." This fact, in itself, affords strong evidence in favor of my view that proteids are supplied to the tissues in the form of leucocytic granules, since this conception involves the ingestion by intestinal leucocytes of the cleavage-products from the alimentary canal.

It is but normal, under these conditions, that these products should be absent from the blood and lymph streams. Indeed, Howell[17] states that: "The form in which proteid is absorbed remains . . . . a mystery."

Twenty-five years ago Hofmeister[18] compared the leucocyte to the red blood-corpuscle, the white cell carrying *peptones* from the intestinal wall to the tissues, while the red cell carried oxygen to the latter. Laboring, however, under the impression that peptones reached the tissues as such and in *fluid* form, being liberated by the leucocytes in some unexplained way, he was unable to defend his theory successfully, and it is now but rarely referred to. A view similar to Hofmeister's was recently (1905) advanced by Pavy.[19]

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[14] Moore: Schäfer's "T. B. of Physoil.," vol. i, p. 432, 1898.

[15] Brubaker: "Human Physiology," eleventh edition, p. 115, 1902.

[16] L. Mendel: Med. News, May 20, 1905.

[17] Howell: "T. B. of Physiol.," p. 716, 1905.

[18] Hofmeister: Zeit. f. physiol. Chem., Bd. iv, S. 253, 268, 1880; Bd. v, S. 127, 1881; Bd. vi, S. 69, 1882.

Hofmeister's view was opposed mainly by Neumeister[20] and Heidenhain,[21] but on very weak grounds. Moore,[22] for instance, reviewing the evidence against Hofmeister's contention, says: "In the first place proteid is not absorbed to any appreciable extent by the lymphatics." But this only shows that it is not their function to do so; granular leucocytes, which are *known* to contain *peptones*, being present in the intestine, thus become the normal absorbents. The second reason adduced is that "albumoses are not changed, as Hofmeister himself has shown, in the blood, which contains plenty of leucocytes." This only proves that it is the function of the leucocytes to absorb albumoses in the intestinal canal but nowhere else, and that it is within these cells that the albumoses are changed. The third reason is that "Heidenhain has shown that the amount of leucocytes in the wall of the intestine (and the amount of active mitosis in these) is too small to render them adequate for the purpose." This is an invalid conclusion unless Heidenhain can give the actual number required *during* the digestive process, and one in fact contradicted by more recent observations, as we shall see. The fourth reason is that Shore[23] has shown that "after slow injection of a small amount of peptone (.049 gramme) into a lymphatic of the hind-limb in a dog, this can be detected again in the course of twenty minutes in the chyle flowing from a fistula of the thoracic duct, showing that it has traversed the lymphatic system unchanged." This merely affords proof that the lymph—and, I may add, the blood—are not media in which the *digestive* leucocytes ingest peptones, and that the only organs in which they do so physiologically are those of the alimentary canal, viz., the stomach and intestinal canal.

Hofmeister based his conception that these cells carried peptones from the intestine to the tissues upon (1) the presence of an enormous number and active proliferation of leucocytes in the intestinal wall during proteid absorption; (2) the increase of leucocytes in the blood-stream, which follows a proteid meal; and (3) the marked decrease of leucocytes in the *intestinal canal during fasting. On the other hand, he found no peptone in the blood-plasma*, and it is now a recognized fact that neither peptones nor albumoses appear as such in the blood. Indeed, when injected into the latter, it is not assimilated and is excreted in the urine (Bunge). Hofmeister also found peptones in blood-clots where leucocytes had accumulated, and a large amount of peptones in the spleen where these cells were correspondingly numerous. Moreover, Pohl[24] observed an increase of leucocytes in the intestine during digestion when the meal was rich in proteids, but not during the digestion of carbohydrates, fats, salts and water. He found that this increase during the digestion of proteids was due to cells which migrated from the intestinal wall. He also noted a very large increase of leucocytes in the intestinal veins during the digestion of a meal rich in proteids, over and above the normal number of cells in the corresponding arteries.

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[19] Pavy: Transvaal Med. Jour., Oct. 1, 1905.
[20] Neumeister: Zeit. f. Biol., Bd. vi, S. 277, 1888.
[21] Heidenhain: Arch. f. d. ges. Physiol., Bd. xliii, Suppl., S. 69, 1888.
[22] Moore: *Loc. cit.*, vol. i, p. 441.
[23] Shore: Jour. of Physiol., vol. xi, p. 553, 1890.

Furthermore, the cells are traceable beyond the intestinal walls. Goodall, Gulland and Noël Paton[25] found experimentally that there occurs "during digestion a slight preliminary fall in the total number of leucocytes in the blood-stream" (which points to a possible concentration of the appropriate leucocytes towards the intestinal structures); that "a fairly regular rise in the total number of leucocytes then follows and the maximum in about four hours after food"; that the increase "is due (*a*) to a lymphocytosis which is very constant as regards its incidence and degree, (*b*) in the majority of cases to a polymorphonuclear leucocytosis." Cabot[26] also states that the increase of leucocytes during digestion is a polymorphonuclear leucocytosis. As polymorphonuclears are all granulation-forming cells, it is evident that such cells migrate to the intestine. In the first volume, I attributed to neutrophile leucocytes the rôle of taking up food-products from the intestine and showed that as lymphocytes they could originate from the lymphatic glands of the intestine. This is sustained by Gulland's[27] researches, which have shown that "lymphocytes are the precursors of all forms," and Escherich and Schurg's[28] *conclusion* that *lymphocytes* are polynuclear leucocytes with neutrophile granulations. Neutrophiles, as is well known, are by far the most numerous of the leucocytes found in the blood.

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[24] Pohl: Arch. f. exp. Path. u. Pharm., Bd. xxv, S. 31, 1888.
[25] Goodall, Gulland and Noël Paton: Jour. of Physiol., vol. xxx, p. 1, 1903.
[26] Cabot: "Clinical Examinations of the Blood," 1901.

Do leucocytes ingest materials in the intestinal canal?

The investigations of Macallum[29] were briefly reviewed in the first volume. This observer having administered albuminate of iron to animals, found that this metal was "deposited *in* leucocytes." These iron-laden cells were found "between the epithelial cells of the tips of the villi," and even more loaded ones were observed to "form a cap, as it were, for the extreme end of the lacteal vessel." He remarks in this connection that "the iron of these cells originates from the food in great part, for if the animal be kept without food for a week, the tips of the villi give but a feeble reaction." Animals that had fasted about four days were fed with commercial peptonate of iron, 100 to 200 grains being given daily for three days. The intestinal mucosa down to the distal end of the small intestine became black when placed in an ammonium sulphide solution, thus showing that the iron had been taken up throughout the entire length of the small intestine. The leucocytes were again found on the tips of the villi, but "others were massed below and in great numbers, and a large number had wandered *between* the epithelial cells in such a way as, in many of the villi, to displace and distort the cells." In an illustration he shows three cells, "in two of which the inner ends appear loaded with iron;" these were fixed "*in the act of transferring*" this metal "to the underlying tissue." This evidently applies to food-stuffs as well, for Asher and Erdely[30] found that while proteids, fats or carbohydrates were being fed to rats, the number of leucocytes in the villi was increased.

Macallum's observations were confirmed experimentally by Cloetta.[31] They not only support those of Hofmeister and

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[27] Gulland: Jour. of Physiol., vol. xix, p. 385, 1895-96.
[28] Escherich and Schurg: cited by Einhorn: Post-Graduate, July, 1904.
[29] Macallum: Jour of Physiol., vol. xvi, p. 268, 1894.
[30] Asher and Erdely: Centralbl. f. Physiol., Bd. xvi, S. 705, 1903.
[31] Cloetta: Arch. f. exp. Path. u. Pharm., Bd. xl, S. 29, 1897.

Pohl, but are themselves indirectly sustained by Metchnikoff,[32] who found that however introduced into the body—by way of the skin, the peritoneum, the blood, etc.—soluble preparations of iron were taken up by leucocytes. Kobert[33] also observed that a soluble saccharate of iron was at once absorbed by these cells.

Macallum noted, moreover, that "in all the preparations, the epithelial cells themselves were comparatively free from the iron compound," and that in sections of the small intestine of lake lizards, fed on iron albuminate, the leucocytes were "loaded with an excess of iron, so much so that the ammonium sulphide gave them the appearance of huge collections of greenish-black granules." That the epithelial cells only play a secondary rôle in the process of absorption is also shown by the fact that Hochhaus and Quincke[34] found in a series of micro-chemical experiments that the iron albuminate was precipitated in the form of granules among the epithelial cells of the duodenum, and that leucocytes then passed these granules to the center of the villi. In Macallum's illustration the actual transfer is clearly depicted. Macallum then found the iron-laden leucocytes beyond the villi, *i.e.*, in their venules, in the capillaries of the liver, the spleen, etc., a fact which shows that these cells are capable of taking up a substance in the intestine and of transferring it to the tissues.

This process is also exemplified by the absorption of fats. Thus, in the first volume (1903), I stated that "while leucocytes which ingest proteids from the intestinal food-stuffs pass between the epithelial cells and enter the venules, the leucocytes which ingest fats only carry the latter from the inner limits of the epithelial cells to the interior of the lacteal, and deposit them therein," and that other leucocytes took them up and carried them to the tissues. Schäfer (1885) had previously regarded leucocytes as the agents in fat absorption, while Reuter (1902) found, as stated by Ferguson,[34a] fat droplets "in the tissue spaces as well as in the *lymphatic corpuscles* of the diffuse lymphoid tissue." As the latter author remarks, this fact "would seem to indicate that other agencies aid in the transit of the fat from the epithelium to the lacteal than are accounted for by the purely mechanical theory of Schäfer." In truth, Schäfer's view differs from mine only in that he observed the first part of the process, *i.e.*, that "leucocytes by their amœboid activity, include the emulsified droplets in the intestinal lumen and convey them into the substance of the villi;" while mine is supplemented by the second phase of the process, that previously witnessed by Reuter, the "lymphatic corpuscles" being the leucocytes which I had traced to the thoracic duct and thence to the tissues.

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[32] Metchnikoff: Annales de l'Inst. Pasteur, vol. viii, p. 706, 1894.

[33] Kobert: Arb. d. pharmakol. Inst. z. Dorpat, S. 123, 1893 u. 1894.

[34] Hochhaus and Quincke: Arch. f. exp. Path. u. Pharm., Bd. xxxvii, S. 159, 1896.

[34a] Ferguson: "Normal Histology and Microscopical Anat.," p. 296, 1905.

Referring to these cells in his text-book of physiology, Noël Paton writes: "During the digestion of proteids the number of leucocytes is enormously increased, sometimes to more than double their previous number, and in all probability *it is they which carry the products of digestion from the intestine.*" This physiologist also says, however: "By breaking down in the blood-stream they probably set free the proteids for use in the tissues." We have just seen that the leucocytes need not break down, while, as I pointed out two years before Paton's work was published, they convert *the products of proteid digestion into granulations* and carry the latter to the tissue cells. I wrote at the time that leucocytes thus "supply the entire organism with the agencies which combine with the oxidizing substance [now adrenoxidase] to insure the continuation of life and the efficiency of all organic functions."

If now we gauge the importance of these facts by the multiplicity of the substances which leucocytes are able to ingest and digest, their ability to take up peptones as well as iron in the intestine asserts itself. J. Carles[28] (1904) refers to the rôle of these cells in the body as "immense." "Nothing escapes these scavengers of the economy," says this author, "muscular fibers, red corpuscles, weakened leucocytes are themselves devoured and destroyed." He also writes: "Leucocytes, in fact, thanks to the ferments they contain, are also endowed with a most active *transforming* activity. A given toxic substance modified by them becomes capable of acting as their own food and likewise as *food for the entire organism.*" Ehrlich considers the granulations of his *mastzellen* as nutritive reserves which these, and perhaps other leucocytes, transfer to the connective tissue spaces, where, according to his view, they are supposed to accumulate.

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[28] Carles: *Loc. cit.*, pp. 7 and 9, 1904.

Evidently Hofmeister is no longer alone to speak of the leucocytes as the nutrient cells of the organism. But here it is necessary to recall the misleading feature of his conception: the belief that the leucocytes supplied *liquid peptones* to the tissues. I was first to point out, in the first volume of this work,[36] which appeared in January, 1903, that *peptones* engulfed by leucocytes in the intestine were *converted* into products suitable for assimilation by the tissue cells, this conclusion being based on the foundation upon which Carles also poises his statement, viz., the wonderful "transforming activity" of which leucocytes are capable in the course of their function as phagocytes. I then submitted[37] the conclusion that "the granules in leucocytes are the products of an *intracellular metabolic process* and represent a true secretion."

As I have previously stated, the intestinal digestive process is continued in the leucocytes. The end-product of the intracellular digestion is then built up, and gradually transferred to the periphery of the cell, as explained in the first volume. That the intracellular digestive process is similar to that in the intestine is emphasized by the fact that, as shown below, leucocytes contain the constituents of the pancreatic juice, *i.e.*, the various zymogens and the two components of enterokinase, including adrenoxidase.

The presence of *adrenoxidase* is demonstrable in various ways. In the first volume[38] I stated—Ehrlich having found that the essential conditions to methylene-blue staining were "oxygen saturation and alkalinity" (Barker)—that the fact that leucocytes took this stain showed they contained the oxidizing substance and blood salts. I sustained this conclusion by showing that other stains endowed with reducing properties were taken up by leucocytes. That these cells contain the oxidizing substance is conclusively shown, moreover, by the fact that Portier[39] found that leucocytes contained "oxidase" as shown by the guaiac test, an observation confirmed by Brandenburg.[40] M. Labbé[41] states that "the coagulating ferment of the blood, fibrin-ferment, is secreted by leucocytes," and he refers to Hewson,[42] Brücke[43] and Glénard,[44] as having demonstrated this fact experimentally. We have seen that fibrin-ferment as shown by Arthus gives the guaiac-blue test. Labbé also states that the researches of Portier, Salkowski, Abelous and Biarnès and Brandenburg have shown the existence of oxidizing ferment, oxidase, in the white corpuscles.

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[36] *Cf.* vol. i, p. 663 *et seq.*, in the first three editions.
[37] *Cf.* vol. i, p. 662, in the first three editions.
[38] *Cf.* vol. i, p. 540, in the first three editions.

The presence of *nucleo-proteid* in leucocytes, whether as such, or in the form of its antecedents—the phosphorus-laden side-chain which, by combining with a proteid nucleus, forms this body (Kossel)—is also evident. Thus, as stated by Schäfer,[45] "in plasma obtained by subsidence of the corpuscles, there is most nucleo-proteid in the lower layers which contain most leucocytes; and least in the upper which contain very few." Again, we have seen that nucleo-proteid, as shown by Stassano and Billon,[46] was present in enterokinase. So closely is this reproduced in leucocytes that Delezenne,[47] after a series of experiments, concluded that the "cytase" of leucocytes and enterokinase were identical.

The presence of *trypsin* and other ferments in leucocytes is now recognized as a fundamental feature of phagocytosis. Metchnikoff's "cytase" is regarded by him and by Bordet and others, as a trypsin; Kanthack and Hardy also attribute the proteolytic activity of leucocytes to soluble ferments. The more recent writers refer increasingly to the presence in leucocytes of such a ferment. Thus, Bulloch states[48] that "thousands of facts point to the conclusion that our leucocyte-forming tissues are our great defensive organs against parasitic invasions," and Beattie,[49] referring to leucocytes, says, "the cells act as phagocytes. They englobe, and by a special secretion or ferment digest other cells or bacteria," etc. That trypsin is the bactericidal agent of the intestinal tract has been shown by Charrin and Levaditi, Zaremba and others, as stated in the first volume. Again, while Weil and Clerc[50] write that "leucocytes do more than englobe bacteria; they submit them to a true process of digestion," M. Labbé[51] says, after referring to the oxidase, fibrin-ferment, etc., found in these cells: "They contain, moreover, a *fibrinolytic* ferment (Leber, Achalme), a casein ferment, a ferment analogous to *trypsin*, a *glycolytic* ferment (Arthus), an *amylolytic* ferment (Rossbach, Zabolotny, Tarchetti), a *lipasic* ferment, which as shown by Poulain plays an important rôle in the assimilation of fats"—briefly all the hydrolytic ferments of the pancreatic juice, and, therefore, the various triads enumerated at the end of the preceding chapter.

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[39] Portier: Thèse de Paris, 1897.
[40] Brandenburg: Münch. med. Woch., Feb. 6, S. 183, 1900.
[41] Labbé: "Le Sang," p. 42, 1902.
[42] Hewson: Sydenham Edition, London, 1846.
[43] Brücke: Arch. f. path. Anat., Bd. xii, S. 81, 172, 1857.
[44] Glénard: Bull. de la Soc. Chim., T. xxiv., 1875.
[45] Schäfer: *Loc. cit.*, vol. i, p. 165.
[46] Stassano and Billon: *Loc. cit.*
[47] Delezenne: C. r. de la Soc. de biol., pp. 283, 591, 893, 1902.
[48] Bulloch: Brit. Med. Jour., Sept. 10, 1904.
[49] Beattie: *Ibid.*, p. 596.

The analysis of the question being continued under the next heading, the following are submitted as preliminary conclusions: (1) *that the products of gastro-intestinal digestion, i.e., the peptones, are not, as now taught, absorbed as such by the intestinal mucous membrane;* (2) *that they do not, as now believed, enter the fluid portion of the blood and lymph;* (3) *that they are taken up from the intestinal canal by leucocytes—the digestive leucocytes—which then enter the circulation;* and (4) *that after terminating the digestion of peptones ingested by them, the leucocytes convert the end-products into granulations, i.e., into a compound suitable for assimilation by the cells of the body at large.*

THE GRANULATIONS OF LEUCOCYTES AS THE GRANULES (MICROSOMES) OF TISSUE-CELLS.

The lymphatic system, as is well known, is the intermediary through which the tissues receive their nutrient substances. "In order to nourish the tissues of the body," writes Isaac Ott,[52] "the plasma of the blood is constantly being osmosed through the capillary walls into spaces between the cells of the tissues. Each cell is thus bathed in a plentiful supply of plasma, from which it absorbs what is needed for its nourishment. This escaped blood-plasma, together with some

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[50] Weil and Clerc: "La leucocytose en clinique," p. 157, 1904.
[51] Labbé: *Loc. cit.*, p. 42.
[52] Isaac Ott: "T. B. of Physiol.," p. 115, 1904.

white cells which have found their way *into the spaces*, constitute the lymph." Starling[53] also concludes that the only way by which the tissues can obtain their supply of proteid is by this process.

In the light of the evidence submitted in the first volume and in the foregoing section, the granulations of the leucocytes—the white cells referred to by Ott—are distributed to the tissue-cells. This necessitates their migration through the walls of the blood-capillaries into the lymph-spaces. As is well known, Cohnheim showed that leucocytes did so in the course of inflammatory processes—an established fact. Now, while Starling states that "the tissue spaces, which are filled with lymph, are always found in association with connective tissue," Gulland[54] witnessed, and illustrates in his paper, a leucocyte "fixed in the act of passing through a narrow hole between two bundles of connective tissue and dragging behind it a large number of granulations in a network of fibers." The cell was evidently entering the lymphatics to become one of the many found therein, which include, as stated by Klein,[55] "granular oxyphile, basophile and *amphophile* cells,"—the amphophiles being the neutrophiles which I regard as nutritive leucocytes. The fact that leucocytes can secrete granules in lymph is shown by the behavior of these cells in the alimentary canal. Thus, while Hardy and Wesbrook,[56] we have seen, observed that leucocytes "within the epithelium or the lumen of the gut" showed a marked diminution or complete disappearance of their granulations, Hoppe-Seyler[57] found that the intestinal fluid, apart from its ferments, "was identical with that of the blood-plasma, and of lymph."

Again, there is a distinct relationship between the digestive leucocytosis and the lymph wave accompanying the digestive process. The correspondence between the fluctuations of activity of the digestive process and the amplitude of the lymph wave was recently emphasized by the researches of G. Oliver,[58] which showed among other facts: "that as the digestive wave

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[53] Starling: Schäfer's "T. B. of Physiol.," vol. i, p. 311, 1898.
[54] Gulland: Jour. of Physiol., vol. xix, p. 385, 1896.
[55] Klein: "Elements of Histology," 1898.
[56] Hardy and Wesbrook: Jour. of Physiol., vol. xviii, p. 490, 1895.
[57] Hoppe-Seyler: Physiol. Chemie. S. 27, Berlin, 1881.
[58] G. Oliver: Lancet, Oct. 3, 1903.

develops the blood becomes more concentrated; that the ingestion of food produces a rapid flow of lymph into the tissue spaces; that there is complete agreement between the blood-pressure and the exudation of lymph," and finally that "the to-and-fro transfers of fluid from the capillary to the tissue spaces constitute a circulation which appears to suffice for all the requirements of metabolism while the body is in a state of rest." That this coincides with a corresponding increase of leucocytes and their products is shown by the familiar digestive leucocytosis which is especially marked after the ingestion of proteids. Thus, as Hammarsten[59] states, the number of leucocytes may be increased "after a meal rich in *proteid.*"

That the granulations of leucocytes are present in all tissue-cells and that they constitute therein and in cells in general what has been termed their "granules" or "microsomes," is sustained by considerable direct and indirect evidence.

It is now generally recognized that, notwithstanding the complex functions which it fulfills in the body, a protoplasmic cell is but a counterpart of a multitude of similar forms, both vegetal and animal, that lead an independent existence as isolated individuals, viz., unicellular organisms. The amœba is an example of this type, the prototype of our mobile, flowing, leucocytes, as well as of our stationary cells—the muscle-cell, the hepatic cell, the nerve-cell, etc.

"It has long been known," says Verworn,[60] "that roundish granules of different sizes are of wide occurrence within cells, lying in an apparently homogeneous ground substance; they have been termed elementary granules, granula or microsomes." . . . . . . "In many cases only a few such granules are present in the cell; in other cases, the whole cell is thickly filled with them, so that the ground substance between them almost disappears." We are evidently dealing with an important feature of vital functions. E. B. Wilson,[61] for example, places the cell-theory "beside the evolution theory as one of the foundation stones of modern biology," and characterizes the

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[59] Hammarsten: "T. B. of Physiol. Chemistry," fourth edition, p. 268, 1904.
[60] Verworn: "General Physiology," p. 63, 1899.
[61] E. B. Wilson: "The Cell in Development and Inheritance," New York, 1897.

granule or microsome as "*the most fundamental question of cell-morphology.*"

Its importance is further shown by the fact that Herbert Spencer attributed to these granules the phenomena of regeneration, development and heredity; that Darwin accorded them an equally prominent rôle in his theory of pangenesis, and that they were likewise regarded as living elements by many other distinguished investigators, including Haeckel, de Vries, Hertwig and Whitman. Indeed, they were the *bio*phores of Weismann, the *bio*plasts of Beale, the *bio*gens of Verworn: they were also the renowned microzymas of Béchamp and Estor which long held sway against Pasteur, and which even now constitute the strongest weapon of the defenders of the theory of spontaneous generation.

The grouping of so many conceptions normally suggests a kinship between them all. Even apparently opposed views assume this relationship, if, in accord with my own view, the leucocytic granulations are considered as nutrient particles which constitute the essential living elements of the cell. This is well shown by the following lines of Herbert Spencer's, quoted from the last edition (1898) of his Principles of Biology: "What these granules or microsomes are—whether, as some have contended, they are the essential *living elements* of the protoplasm, or whether, as is otherwise held, they are *nutritive particles*, is at present undecided."

Even the limited evidence and conclusions I have submitted so far suffice to point strongly to the leucocyte granulations as the "nutritive particles" referred to. We will now see that these granulations and the cellular "granules" correspond in every way.

The nucleus of all cells is composed mainly of two substances, the *chromatin*, thus termed because it is deeply stained by appropriate dyes, and the *nuclear sap*, which takes a lighter tint. "The chemical composition of chromatin is highly complex," says Spencer,[62] "and its complexity, apart from other traits, implies relative instability. This is further implied by the special natures of its components. Various analyses have shown that it consists of an organic acid (which has been called nucleic acid) *rich in phosphorus** combined with an albuminous substance: probably a combination of various proteids. And the evidence, as summarized by Wilson, seems to show that where the proportion of phosphorized acid is high the activity of the substance is great; while, conversely, where the quantity of phosphorus is relatively small, the substance approximates in character to the cytoplasm. Now, (like sulphur, present in the albuminoid base) phosphorus is an element which, besides having several allotropic forms, has a *great affinity for oxygen;* and an organic compound into which it enters, beyond the instability otherwise caused, has a special instability caused by its presence. The tendency to undergo change will therefore be great when the proportion of the phosphorized component is great. Hence the statement that 'the chemical differences between chromatin and cytoplasm, striking and constant as they are, are differences of degree only;' and the conclusion that *the activity of the chromatin is specially associated with the protoplasm.*"

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[62] Spencer: "Principles of Biology," vol. I, p. 259, New York, 1898.

This recalls strikingly the rôle I have ascribed to nucleo-proteid, owing to the large proportion of phosphorus its nuclein contains, and the intense affinity of this element for oxygen. Indeed, it is clear from the above that both *nuclein* and *proteid* are present in the cell, in the identical form in which we found these bodies elsewhere, *i.e.*, as granulations. Now, the granulations of neutrophile leucocytes, which I regard as the nutritive cells, are nucleo-proteid bodies. This was first suggested by Sherrington, then demonstrated by Milroy and Malcolm,[63] whose methods are given in detail in the first volume.[64] Again, Stewart,[65] alluding to the origin of nucleo-proteid, writes: "In shed blood, the *only possible sources* of nucleo-proteid, so far as we know, are the corpuscles and the blood-plates." After dismissing the red corpuscles, he adds: "We have left over the leucocytes and the platelets. The latter are said, and the former *are known* to yield nucleo-proteid when they are broken up in the laboratory."

That leucocytes are capable also of carrying their product to all parts of the organism is an obvious corollary of their well-known migratory habits, and of the remarkable ease with which they alter their shape in order to pass through minute openings. We have seen that they do so dragging their nucleo-proteid granulations behind them, and that they secrete them. M. Labbé,[66] in common with others, writes: "In respect to foods," the leucocyte "serves, to a degree as yet impossible for us to estimate, for their absorption and transformation, and for their distribution to the cellular elements in need of them." But *what* do they yield to these elements? This question has remained unanswered. As shown above, the only products to which evidence points are their nucleo-proteid granulations.

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* All italics are my own.—S.

[63] Milroy and Malcolm: Jour. of Physiol., vol. xxiii, No. 3, p. 217, 1898.

[64] *Cf.* vol. i, p. 693, in the first three editions.

[65] Stewart: "Manual of Physiology," fourth edition, p. 41, 1900.

Another question imposes itself in this connection, however: What is the identity of the plasmatic proteids which, according to the prevailing doctrine, are thought to reach the tissue-cells and to be absorbed by them? The answer is embodied in evidence already submitted, viz., that *there are two kinds of nucleo-proteids*, one for the *tissue-cells*, that alluded to above, and one for the *blood* itself (the fibrinogen to which I have repeatedly referred in the first volume), both secreted by leucocytes. Over thirty years ago Voit[67] showed that the proteid which formed part of the tissue-cells, and which he termed "*organ*-proteid," could not be similar to that present in the blood-stream. The blood proteid he therefore termed the "*circulating* proteid." Liebig, Hoppe-Seyler and Pflüger, in opposition to the additional (and purely theoretical) belief of Voit's that "organ-proteid" had to be dissolved in the plasma and become "circulating" before it could be used in cellular metabolism, showed that "circulating proteid" never underwent *metabolic* changes, and that this rôle was limited to the "organ-proteid." This not only proves that the *plasmatic* proteids are not concerned with tissue metabolism, but it likewise confirms Voit's view as to the presence of two kinds of proteid, *i.e.*, one for the blood-stream and one for the tissues—though both, as interpreted from my standpoint, are products of leucocytes.

Still, the nucleo-proteid destined for the tissue metabolism would be consumed in the oxygen-laden plasma were it not protected during its transit from the intestine to the tissues. The *leucocytes satisfy precisely this need, by keeping their granulations within their cytoplasm, until in contact with the tissues*, where they secrete them. In the first volume, I pointed out *that the leucocytes which secreted "fibrinogen" in the bloodstream likewise did so physiologically as required, their secreted granulations combining with the oxidizing substance (adrenoxidase) as needed to sustain, according to the body's needs, the blood's own temperature.* Here again, the nucleo-proteid granulations are protected by the cytoplasm of the leucocytes until needed.

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[66] Labbé: *Loc. cit.*, p. 39.

[67] Voit: Zeit. f. Biol., Bd. x, S. 202. 1874.

Two tests of the question are necessary, however, to place the conclusions herein submitted on a solid basis: (1) the granules or microsomes of the tissue-cells should react to stains as do the granulations of leucocytes; (2) the tissue-cell granules should be shown to act as nutritive particles in keeping with the leucocytic granulations.

Wilson,[68] referring to the two forms of granules found in the chromatic network of cells, says: "They are sharply differentiated by dyes, the *basi*chromatin being colored by the basic anilines (methyl-green, saffranin, etc.) and other true nuclear stains; while the *oxy*chromatin-granules, like many cytoplasmic structures, and like the substance of true nucleoli (pyrenin), are colored by *acid anilines* (rubin, eosin, etc.) and other 'plasma stains.'" Klein,[69] on the other hand, states, referring to "granular leucocytes," that they "behave differently when subjected to staining with aniline dyes. In some the granules stain readily with *acid aniline* dyes—*e.g.*, eosin—so that they become bright red—eosinophile (Ehrlich) or *oxy*phile cells; in others, the granules stain only in *basic* aniline dyes—basophile cells; in still others they stain both with acid and alkaline aniline dyes—neutrophile or *amphophile*." This applies as well to nerve-cells. Thus, the ganglion-cell "in which," as stated by Ewing,[70] "the chromatic element is in the form of granules irregularly placed through the cell-body," react in the same manner to those reagents. Marinesco[71] found that the "chromophile elements of motor-cells were strongly stained by *basic aniline* reagents,"[71] and Benda[72] observed chromatic granules which stained as do the *baso*philic granulations of leucocytes. Held[73] also depicted granules stained by *acid* anilines, and both Colucci[74] and Heimann[75] observed others which, like *amphophilic* granulations, stained with acid and alkaline dyes. It is evident, therefore, that as far as their reaction to stains is concerned, tissue-cell granules and leucocyte granulations correspond.

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[68] Wilson: *Loc. cit.*, p. 28.
[69] Klein: *Loc cit.*, p. 27, 1896.
[70] Ewing: Arch. of Neur. and Psych., vol. 1, No. 3, p. 263, 1898.
[71] Marinesco: C. r. de la Soc. de biol., Jan. 25, p. 106, 1896.

The second test, *i.e.*, that the granulations nourish the tissue-cells, is no less conclusive. Monti[76] and Lamy,[77] after obstructing the circulation of cerebral vessels by injections of lycopodium, observed a progressive loss of chromatic substance, *i.e.*, of granules, in the dendrites and cell-bodies of the parts deprived of blood. The last-named investigator also observed a gradual loss of chromatic substance in these cells after ligating the aorta. Sarbo[78] noted a gradual disintegration of this substance after ligating the abdominal aorta. Juliusberger[79] obtained a similar effect by compressing this vessel. Ewing[80] verified these results in the human subject, and concluded that "the chromatic structures of these nerve-cells are more immediately affected by changes in their blood supply than by any other influences whose effects upon them have yet been studied." Hodge[81] and Mann[82] observed that "during the repose of the cell, the chromatin accumulates in the nucleus, while during the cell activity this stored-up material gradually disappears."[83] Considered unitedly these facts indicate plainly that it is from the blood and its cells that the nerve-cells receive their chromatic granules, and that their purpose is to nourish these cells.

Chromatolysis, *i.e.*, destruction of the granules, shows, not only that the granules are nutrient bodies, but also that these

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[72] Benda: Neurol. Centralbl., Bd. xiv, S. 759, 1895.
[73] Held: Arch. f. Anat. u. Physiol., S. 396, 1895; S. 204, 1897.
[74] Colucci: Ann. d. Neurol., S. 145, 1896.
[75] Heimann: Virchow's Archiv, Bd. cliii, S. 298, 1898.
[76] Monti: Arch. ital. de biol., S. 20, 1895.
[77] Lamy: Arch. de physiol., T. vii, p. 77, 1895; T. ix, p. 184, 1897.
[78] Sarbo: Neurol. Centralbl., Bd. xiv, S. 664, 1895.
[79] Juliusberger: *Ibid.*, Bd. xv, S. 386, 1896.
[80] Ewing: *Loc. cit.*, p. 410.
[81] Hodge: Jour. of Morph., vol. vii, p. 95, 1892.
[82] Mann: Jour. of Anat. and Physiol., vol. xxix, p. 100, 1894.
[83] Bawden: Jour. of Compar. Neurol., May, p. 242, 1900.

bodies are of external origin. "*Chromatolysis generally begins at the periphery of the cell and in the dendrons,*" says Halliburton,[84] "but in advanced cases the whole cell may be affected." That the morbid progression is inward is obvious. The same author says also that chromatolysis alone, however, "is not indicative of cell destruction," and that "the cell may *recover its functions later when the abnormal condition passes off.*" This further indicates that the granules are nutrient elements, *i.e.*, substances of extrinsic origin and bound therefore to penetrate the cell centripetally, their first contact with it being in the intercellular spaces, where granular leucocytes are often met.

On the whole, the identity of (nucleo-proteid) cell-granules as "nutritive particles," using Spencer's expression, is no longer to be doubted. Ewing, after reviewing the labors of several of the above and other investigators, remarks: "Nevertheless the consideration of more recent data leads irresistibly to the conclusion that the chromatic bodies of the nerve-cells represent a state of physiological nutrition." Referring to Nissl's granules, Halliburton[85] also writes: "It can hardly be denied that the substance of which the granules are composed, forming as it does so large a proportion of the cell-contents, and made of a material in which nuclein is an important constituent, is intimately related to the *nutritional* condition of the neuron."

The most complicated of all cells, the nerve-cell, has been taken as model because it exemplifies better than any other the function of nucleo-proteid granules, *i.e.*, the chromatic bodies. This rôle is common to all cells; thus Hammarsten,[86] referring to the animal cell in general, writes: "The nucleo-proteids take a very prominent place among the compound proteids of the cell." Indeed, this applies to the entire animal scale, down even to the simplest of living things, the protamœba. Though this unicellular organism contains neither nucleus nor contractile vacuole, the same minute nucleo-proteid granules—chromatin—are clearly visible throughout their entire substance. In fact, the same stainable particles are met with in somewhat less primitive forms, some ciliated infusoria—*Oxy-*

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[84] Halliburton: "Biochemistry of Muscle and Nerve," p. 87, 1904.
[85] Halliburton: *Loc. cit.*, p. 87.
[86] Hammarsten: *Loc. cit.*, p. 118.

tricha flava, for example—in which they represent the fragments of broken-up nuclei. In another organism of the same group, *Trachelocerea*, we see the identical stainable granules, but here they are collectively termed a "diffused *nucleus*,"—a nucleus starting from the *periphery* of the cell, where the granules are most numerous, and apparently invading the whole field—the nutrient material penetrating their surface precisely (in the light of my views) as our own cells absorb the nutrient granules supplied to them by leucocytes.

The *Porifera*, a group to which the sponges belong, afford an example of the manner in which the granulations of leucocyte-like cells can subserve nutrition. Thus, Haeckel[87] refers to amœbocytes as "the remarkable amœboid wandering cells, which seem to possess an important physiological function in all sponges." . . . . "Their protoplasm usually encloses," says this distinguished zoölogist, "a variable mass of dark, highly refracting and *intensely staining granules*, and often these enter into the lappet-like processes, or lobopodia of the cell, as in the similar common amœbæ. The amœbocytes of the sponges are *comparable to the leucocytes of the higher Metazoa*." . . . . . . "Their functions are probably multifarious, referring mainly to the nutrition of the sponge. They may be vehicles of food and of reserve nutriments."

The kinship of the amœbocytes with the leucocytes of our own organism becomes striking when the structure of the former is closely examined. Ray Lankester[88] includes among the distinguishing features of the wandering cells of sponges "the quantity of granules with which their cytoplasm is usually packed;" also "the nature of the contained granulations, one kind having coarse, large granules, the other fine granules." He refers to the researches of Fiedler (1888), who describes two kinds of wandering cells, "which he has termed Fresszellen (phagocytes) and Nährzellen (trophocytes) respectively; the former, which occur always near the free surfaces of the sponge body, are concerned more especially with the *ingestion*, and perhaps with the *digestion* of food; the latter, found in all parts, appear to provide for its *distribution*."* We have here a self-evident counterpart of the functions of leucocytes in the highest *vertebrates, as emphasized in the foregoing pages.*

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* The italics are my own.—S.

[87] Haeckel: "Rep. of Challenger Exp.," vol. xxxii, 1889.

[88] Ray Lankester: "Treatise on Zoölogy," Pt. ii, 1900.

The correspondence between so lowly an animal as the sponge and the highest representatives of the zoölogical scale is not invalidated by the fact that the former lives in the seas while the latter include a vast number that lead a purely terrestrial existence. Forty years ago, Claude Bernard[89] taught that the blood of vertebrates represented "an internal medium in which anatomical elements live as do fishes in water." Indeed, man has not severed his connection with the Oceans in which lived the primitive cells from which he sprang; his blood, we shall see,[90] closely approximates sea-water in composition: he merely carries, therefore, a bit of the Ocean within him. But we must not overlook the difference between a free mobile, unicellular organism, the amœba, for instance, and a cell deprived of migratory motions such as the tissue-cell. The one is able to provide itself with sufficient food, not only because it can reach for it with its pseudopodia, but also because it can, by migrating, increase, when necessary and conditions permitting, its food-supply. The sedentary tissue-cell, imprisoned among its kind, cannot thus satisfy its needs, and Nature meets the want by providing both an amœboid messenger, the leucocyte, and the precise food the tissues need, the granule.

Summarized, this evidence, supplemented by that contained in the preceding section and in the first volume, appears to me to warrant the following conclusions: (1) *that the tissue-cells are not nourished as now taught, by peptones carried to them by the blood-plasma;* (2) *that this function is carried on by leucocytes which migrate through the walls of the capillaries with the blood-plasma, to enter the spaces between the tissue-cells;* (3) *that once in the intercellular spaces the leucocytes secrete their granulations;* (4) *that these granulations are the nutritive materials of the tissue-cells;* (5) *that the granulations penetrate the tissue-cells from the periphery and constitute their granules or microsomes.*

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[89] Claude Bernard: Leçons sur les propriétés des tissus vivants," p. 55, Paris, 1866.

[90] *Cf.* this vol., 1267.

THE LEUCOCYTIC FERMENTS AS THE INTRACELLULAR FERMENTS OF TISSUE-CELLS.

Mendel[61] wrote as far back as 1906: "Enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities of cells in almost every feature of metabolism." Indeed, the tissue-cell does not contain the nucleo-proteid only; it embodies, as shown below, the three agents which carry on the digestive process in the alimentary canal, and which jointly constitute an "enzyme" or "ferment," one of the hydrolytic triads.

The presence of the *zymogen* is shown by that of the ferment of which it is the known precursor. Verworn[62] states that ferments "appear in both animals and plants," and that even in "free cells," *i.e.*, unicellular organisms, "the ferments are of great importance for the nutrition of the cell when these organisms, as is the case with the bacteria, come into contact with organic food and are obliged first to liquefy solid food-stuffs in order to be able to absorb them." That this is carried out by a common ferment was recently suggested by S. H. Vines.[63] "All known proteolytic enzymes of plants are tryptic," says this plant physiologist, "though some of them, such as that of *Drosera*, still await further investigation. This suggestion," he adds, "gains in interest when it is borne in mind that *tryptic* digestion is of general occurrence in the animal kingdom, and is apparently the sole process in many vertebrates. It is not improbable that it may be extended into the proposition that tryptic digestion is a property of all living organisms."

That this applies as well to human and other animal tissues is shown in our own literature: "There is no longer any reason to suppose," says Halliburton,[64] "that the ferment at work is pepsin which had been previously absorbed from the alimentary canal, for Hedin and Rowland[65] have shown that the proteolytic ferment which is present in muscle, as in many other animal tissues (spleen, kidney, etc.), is more like *trypsin* than pepsin in its mode of action." Elsewhere, he reminds the reader[96] "*of the existence*" in muscle "*of a proteolytic enzyme*" *and finally states that "glycolysis occurs in many tissues, and* that the agent or ferment to which this is due, is believed by Cohnheim[97] to be rendered active by the internal secretion of the pancreas." That trypsinogen is common to all cells is evident.

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[61] Mendel: Jour. Amer. Med. Assoc., Mar. 24, 1906.
[62] Verworn: *Loc. cit.*, p. 171.
[63] S. H. Vines: Annals of Botany, vol. xv, p. 572, 1901.
[64] Halliburton: *Loc. cit.*, p. 12.
[65] Hedin and Rowland: Zeit. f. phys. Chemie, Bd. xxxii, S. 341, 531, 1901.

The presence of *nucleo-proteid* has been sufficiently emphasized in the preceding section. I showed therein that all cells, from the lowest unicellular organisms up to the highest members of great cell colonies, contained nucleo-proteid granules. I may add the testimony of Chittenden,[98] who likewise wrote: "Nucleo-proteids of various kinds are conspicuous constituents of all cells; they are found in all tissues, in all glandular organs, and their widespread distribution may be taken as evidence of their great physiological importance."

The term "oxidizing substance," we have seen, is synonymous with "oxidase," and, in the higher organisms, with *adrenoxidase.* "It has been positively proved by the researches of Jaquet, Salkowski, Spitzer, Röhmann, Abelous and Biarnès, Bertrand, Bourquelot, DeRey-Pailhade, Medvedew, Pohl, Jacoby, Chadot and Bach, and others," says Hammarsten,[99] "that in the blood and different *tissues* of the animal body, as also in plant cells, substances occur which have the property of causing certain oxidations and are therefore called oxidation ferments or oxidases. Little is known in regard to the nature or the manner of action of these bodies." In the thirteenth chapter[100] I stated that, while Claude Bernard, Pavy and Lépine had observed that blood-plasma could oxidize sugar, Pohl, Spitzer and others had found that intercellular and tissue juices produced a similar effect; that Loew had been led by his researches to conclude that "there does not exist a group of organisms or any organ, or even a single vegetable or animal cell that does not contain some catalase;" and finally that "this general occurrence of catalase in the *organized world* cannot be accidental and must have a certain significance." We have seen also that recently Jolles[101] found that the catalase which decomposes hydrogen peroxide is associated with the red corpuscles. As I have shown,[102] catalase is a name given to adrenoxidase, or its homologue in animals in which adrenals do not exist and in plants, owing to the catalytic properties of its active principle. Adrenoxidase is thus endowed with two properties, viz., that of a catalytic and that of an oxidizing agent. Loew's generalization, therefore, applies to adrenoxidase or its homologue in lower forms. Its presence in the latter is further emphasized by the fact that sponges protect their bodies, according to Ray Lankester,[103] not only by fringes and palisades of spicules, but "also by excretion of poisonous ferments from the surface of the body which have a strongly oxidizing action."

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[96] Halliburton: *Loc. cit.*, p. 31.
[97] Cohnheim: Zeit. f. phys. Chemie, Bd. xxxix, S. 336, 1903.
[98] Chittenden: Boston Med. & Surg. Jour., Aug. 17, 1905.
[99] Hammarsten: *Loc. cit.*, p. 7.
[100] *Cf.* this vol., p. 812.
[101] Jolles: Münch. med. Woch., Nov. 22, S. 2083, 1904.

Not only are the three components of trypsin—the ferment itself in fact—thus shown to be present in all tissue-cells and in all organisms, but tissue-catabolism corresponds in its general characters with the digestion of nucleo-proteids as carried on by trypsin—the hydrolytic triad—in the intestine.

As stated by Barnes,[104] there is a remarkable uniformity in the decomposition of products of all cells. "No matter what the organism from which they are derived," says this plant physiologist, "no matter how simple they are or how complex, when broken up by the process of digestion or by boiling with acids, they yield invariably a series of products which have become in the last few years much better known. These are amino- or amido-acids, such substances as leucin, tyrosin, arginin, glutamin, glycocoll, etc." As this applies to the digestive process in the intestine as well as to artificial digestion, we can conclude that if these decomposition products are also excreted by the tissue cells, these cells are the seat of a digestive process similar to that of the intestinal canal.

That such is the case is shown by the fact that the precursors of urea, which include the amino-acids, can be traced to the tissues. Salkowski,[105] Schultzen and Nencki,[106] and other chemists, have shown that amino-acids are converted into urea during the transit through the body. That the liver is not the only organ in which this conversion occurs, as was formerly believed, may be shown in various ways. Experimental removal of this organ by Slosse,[107] Nencki and Pawlow,[108] and others, failed to arrest the formation of urea, while Kauffmann[109] found that when the liver and kidneys were entirely isolated from the circulation (to which, we have seen, the lymph carries waste-products derived from the cells), the blood was found to contain an excess of urea. This was confirmed by the researches of Wurtz, which showed that under the same conditions, "lymph contains more urea than does the blood of the same individual" (Schäfer[110])—considerably more, in fact, since the ratio is 0.009 parts per cent. in the blood to 0.016 parts per cent. in the lymph.

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[102] *Cf.* this vol., p. 822.
[103] Ray Lankester: *Loc. cit.*
[104] Barnes: Science, vol. xxi, No. 529, p. 241, 1905.
[105] Salkowski: Zeit. f. physiol. Chemie, Bd. iv, S. 100, 1879.
[106] Schultzen and Nencki: Zeit. f. Biol., Bd. viii, S. 124, 1872.

Finally, Halliburton[111] states that "there can be but little doubt that muscular tissue, being our most abundant tissue, is the ultimate source of most of the nitrogenous waste that leaves the body as urea." Indeed, Barnes refers to the ease with which lactic acid (and this applies also to the familiar muscular acid, *i.e.*, sarco-lactic acid) "can be converted into an amido-acid, glycocoll." Chittenden also says:[112] "Muscles, liver, kidneys, lymph-glands, lungs, spleen, etc., all contain proteid-dissolving ferments, and when the tissues are subjected to auto-digestion or autolysis, such products as the amido-acids, leucin and tyrosin, tryptophan, glycocoll, hexone bases or diamino-acids and ammonia result from the breaking down of the various proteids of the tissue." He closes the paragraph with the statement that "the general trend of action with these intracellular proteolytic ferments is *hydrolytic cleavage*, much the same as the influence exerted by mineral acids, or by *ordinary digestive enzymes*."

It is evident, therefore, that the tissue cells are the seat of a digestive process similar to that in the intestinal canal, and that it is carried on by the same hydrolytic triad "trypsin."

Two sources of confusion in the current interpretation of tissue metabolism require attention in this connection. The first of these is the multiplicity of ferments which are thought necessary to explain tissue function—a feature which, in my opinion, accounts for the growing complexity of the problem.

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[107] Slosse: DuBois-Reymond's Archiv f. Physiol., S. 482, 1890.
[108] Nencki and Pawlow: Arch. d. Sc. Med. de St. Petersburg, T. V.
[109] Kauffmann: C. r. de la Soc. de biol., T. xlvi, p. 323, 1894.
[110] Schäfer: *Loc. cit.*, vol. i, p. 182, 1896.
[111] Halliburton: *Loc. cit.*, p. 41, 1904.
[112] Chittenden: Boston Med. & Surg. Jour., Aug. 17, 1905.

Chittenden[113] remarks: "There is practically no process of metabolism so intricate or obscure that it cannot well be explained by the action and interaction of intracellular ferments." The confusing feature just referred to appears, however, when he adds: "New ferments are constantly being discovered, new chemical reactions are being traced to the power of *special* ferments. . . . . . " This applies also to the oxidizing ferments. "Oxidation is preëminently one of Nature's ways of bringing about alteration and decomposition," says the same author, "and in intermediary metabolism especially, oxidative processes must be quite conspicuous. Yet to-day we have accumulated a mass of evidence tending to show that oxidation in the tissues is due primarily to the presence and action of a *row* of more or less *closely related*, though chemically distinct ferments, known as oxidases.* Physiological oxidation, therefore, as it occurs in metabolism, is likewise a result of intracellular ferment action." This corresponds with the prevailing view, the various ferments bearing characteristic names, aldehydase, guanase, tyrosinase, adenase, indolphenol-oxidase, nuclease, etc., etc., according to the substances upon which they act, the organs in which they are found, the organic substance with which they happen to be combined, etc.

At best, this multiplicity of ferments—both proteolytic and oxidizing—can only be assumed, since as recently (1905) stated by Halliburton:[114] "Ferments are substances which have, to a great extent, eluded the grasp of the chemist. All he can say," adds this physiologist, "is that they are probably proteid-like in nature, and in some cases the proteid material with which they are either identical or *united* is, as in the case of *fibrin ferment*, of the *nucleo-proteid* variety." On the other hand, this is a suggestive statement in view of the interpretation of the composition of ferments in general I have submitted in the preceding chapter: viz., that there is *but one true ferment*—that represented by the adrenal active principle of adrenoxidase (or its homologue in organisms deprived of adrenals); that all "ferments" contain nucleo-proteid; and finally that the specific action of any "ferment" is due, not to a specific ferment, since *there is but one "ferment of ferments,"* but to the zymogen which the triad termed "ferment" happens to contain.

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* The italics are my own.—S.

[113] Chittenden: *Loc. cit.*

[114] Halliburton: *Loc. cit.*, p. 30,

Once fully apprehended, this simplified conception of the composition of ferments will tend to eliminate many of the obstacles met with when any attempt is made to interpret clearly the intrinsic processes of tissue-metabolism—obstacles which have made it impossible, so far, to discern the true nature of this process. Besides supplying a logical explanation of the manner in which oxygen is supplied to the tissues (the process I have submitted in the thirteenth chapter of this work) we would not be constantly confronted with new "ferments," but with combinations of known tangible bodies, whose chemical properties have been thoroughly scrutinized—all endowed with their quality as a "ferment" by the "ferment of ferments."

Examples are not lacking in which these principles are applicable. Thus, we have seen that Pawlow's enterokinase and Bayliss and Starling's secretin are not ferments, but that they contain adrenoxidase. Cohnheim's "muscle ferment" need only be adrenoxidase to cleave sugar when combined with the secretion of the islands of Langerhans if either the latter or the adrenoxidase contain nucleo-proteid. Finally, Cohnheim's erepsin need not be a "ferment," since, as shown by various investigators, it has the same properties as trypsin; it may be, therefore, only the proteolytic triad known under the name of "trypsin." Yet, Cohnheim holds, on good ground, that erepsin is not trypsin, and that it is endowed with other properties. So is the pancreatic juice endowed with properties other than those of trypsin—those it receives from zymogens other than trypsinogen, and which are all, we have seen, taken up by the digestive leucocytes. It may thus happen that erepsin will prove to be an aggregate of all the hydrolytic triads—proteolytic, amylolytic, lipolytic, glycolytic, etc.—which bathe the intestinal mucosa, and which, through the intermediary of the leucocytes, reach the tissue-cells, to carry on therein a function similar to that performed by them in the intestinal canal, *i.e.*, digestion by hydrolysis, but having as object in the tissue-cells, the breaking down of worn-out elements.

The second misleading feature now suggests itself: the prevailing belief that the tissue-cells themselves are a source of the "intracellular ferments," and that the intrinsic processes of the cell are ascribable to the presence of a large number of such ferments.

This doctrine has also done much to obscure our knowledge of cellular metabolism by suggesting fictitious functions in the tissue-cell, thus defeating any attempt to discover the sequence of events in the interchanges of which it is the seat. Suggestive in this connection are the following lines by Moore in an analysis of the subject:[115] "Much has been made of the fact that intracellular enzymes have been isolated from living cells which are capable of producing actions hitherto only observed in the presence of the cell, and it has been surmised that all, or nearly all, the chemical activity of the cell may be due to the action of a large number of such intracellular enzymes." . . . . "Without disparaging the importance and value of such work of separation of intracellular enzymes, it may, however, be urged that there is in such a view no explanation of the phasic activity of the cell, no taking into account of the action of the living cell in co-ordinating, so to speak, the myriad activities going on within it whereby the whole process is regulated."

In the light of all the facts submitted so far in this work regarding the rôle of leucocytes in the nutrition of the tissue-cell, the coördination of the various phases of its life-cycle assumes a normal sequence. The leucocyte not only supplies the "nutritive particles," as Herbert Spencer calls them, thus satisfying the constructive or anabolic phase of the process, but also the hydrolytic enzymes necessary to break down the worn-out nutrient material and prepare it for elimination—the catabolic phase of the process.

A question at once imposes itself, however, in this connection. We are dealing now with the tissue-cells of highly differentiated animals in which the pancreas affords an endless supply of zymogens for the elaboration of "ferments," which the leucocytes transfer to the cells. How can we account for the presence of these same enzymes—or aggregate of enzymes characterized as "trypsin"—in an animal devoid of pancreas, down, in fact, to the lowest in the zoölogical scale, the unicellular organisms? Even the latter differs in no way, as to the manner in which its life-cycle is sustained, from the tissue-cell of the highest of vertebrates, man. Although it has to provide for itself, it acquires from the organic materials it engulfs in its protoplasm the three bodies required to build up its "ferments," and which, we have seen, are present in all living structures.

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[115] Moore: Hill's "Recent Advances in Physiology and Bio-Chemistry," p. 11, 1906.

All this clearly points to a common governing principle in all organic life concerning the manner in which a living cell acquires the ferments which carry on its metabolism, viz., combined with the food materials it ingests. It is evident that since, as we have seen, it is the function of the digestive leucocytes to provide the tissue-cells their nutrient materials and the hydrolytic ferments required to break the latter down when they are no longer of use, these ferments cannot be said to originate in the tissue-cells themselves, but in the digestive apparatus from which the leucocytes obtain them.

Since I first advanced these views in 1903, the brilliant labors of Abderhalden[115a] have contributed much confirmatory evidence. "Each separate cell with very few exceptions," writes this physiclogical chemist," disposes of the same or similar ferments as those secreted by the digestive glands in the intestinal canal." As to the manner in which the ferments are conveyed to the tissue-cells, he says: "Many facts accord with the suggestion that the leucocytes play a part in this connection."

In brief, it seems to me permissible to conclude: (1) *that the tissue-cells do not contain, as now believed, a large number of special ferments differing from those found in the intestine;* (2) *that the tissue-cells of all living organisms contain the three constituents of at least one hydrolytic triad, trypsin, including adrenoxidase, the active principle of which confers upon the latter its properties as a ferment;* (3) *that whereas in*

[115a] Abderhalden: "Defensive Ferments," third edition, 1914.

the intestine and in the digestive leucocytes, trypsin hydrolyses food-proteids prior to their transformation into assimilable granules (anabolism), in the tissue-cell it hydrolyses worn-out proteid granules or chromosomes to convert them into eliminable waste-products (catabolism); (4) that the trypsin or any other hydrolytic ferment found in tissue-cells does not originate in these cells, but from the digestive apparatus through the intermediary of the digestive leucocytes.

THE GRANULATIONS OF LEUCOCYTES AND ADRENOXIDASE IN THE FUNCTIONS OF THE NERVE-CELL.

"What the nerve-impulse actually consists in we do not know," says Stewart.[116] Nor have the more recent labors solved the problem.

We have just seen that the chromatin granules, which correspond chemically and tinctorially with the nucleoproteid granulations of leucocytes, are also present in the nerve-cells. Again, in the first volume[117] I pointed out a fact which seemed to me capable of affording a clue to the nature of the nerve-impulse, viz., that the oxidizing substance—the adrenoxidase—circulates in the axis-cylinders of nerves, the cell-bodies and their protoplasmic processes or dendrites, and other nerve-structures, and that the nervous system, as far as the plasma is concerned, is *an extension of the general circulation*, thus constituting what might be termed the intraneural circulation.

That the various nervous structures referred to are longitudinal channels or canaliculi similar to capillaries, and that the blood-plasma circulates in these channels, is sustained by considerable evidence.

Holmgren[118] found that the reticular network of all ganglion-cells was, in reality, a system of lymph-canaliculi and that the nucleus itself received two delicate vessels. This was confirmed by Studnickal, Bethe and others. Donaggio[119] conducted similar researches, using, however, material from various parts of the brain and spinal system. He not only confirmed the findings of his predecessors, but found that the distribution and general characters of the minute canaliculi were identical in all types of cells, the only variations being in the caliber of the canaliculi, these minute channels being somewhat larger in some cells than in others. That it is not lymph, however, as these authors believe, that circulates in the ganglionic canaliculi, and that it is the blood-plasma—its vascular homologue—is shown by the earlier (1886) experiments of Adamkiewicz.[120] This observer found that injections into blood-vessels caused the plasma alone, *i.e.*, blood-plasma without blood-corpuscles, to penetrate minute capillaries which coursed in ganglionic cells.

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[116] Stewart: "Manual of Physiology," fourth edition, p. 592, 1900.
[117] *Cf.* vol. i, pp. 532 to 590.
[118] Holmgren: Anatom. Anzeiger, Bd. xvi, Nu. 7, S. 161, 1899.
[119] Donaggio: Rivista sperimentale, Fasc. i, 1900.

Zoölogy affords many examples in which the blood-plasma circulates in the nerve ganglia. This is best shown in animals whose blood contains no red corpuscles and in which the hæmoglobin is dissolved in the plasma. Thus, Ray Lankester[121] found that in the sea-mouse the chain of nerve ganglia was a bright crimson color, the hue in the supra-œsophageal ganglion being as intense "as a drop of fresh human blood," the color impregnating "the nerve itself." Gamgee[122] also states that "hæmoglobin has been found diffused in the substance of the nervous tissue," and that Hubrecht[123] "found hæmoglobin in the red-colored cerebral ganglia of certain Nemertine worms, which possess no colored blood-corpuscles."

Pathology supplies striking testimony in the same direction. Although the fact that the toxin of tetanus affects mainly the central nervous system has been known a long time, the manner in which it reaches the cellular elements has only been established within the last few years. Marie and Morax, in 1902,[124] found that when this toxin was injected into the tissues it entered the blood. Thence it passed into the motor and vasomotor nerves, beginning with the peripheral nerve endings, and steadily progressed upward by way of the *axis-cylinders,* until the central nervous system, cord, pons, medulla, etc., were saturated. While motor nerves were found to "absorb" toxin more rapidly than others, the sensory and sympathetic nerve endings were also found to take up portions of

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[120] Adamkiewicz: Neurol. Centralbl., Bd. xix, S. 2, 1900.
[121] Ray Lankester: Proc. Royal Soc., London, vol. xxi, p. 70, 1872.
[122] Gamgee: Schäfer, *Loc. cit.*, vol. i, p. 187.
[123] Hubrecht: Niederland Arch. f. Zoölogie, Hft. 3, 1876.
[124] Marie and Morax: Ann. de l'Inst. Pasteur, vol. xvi, p. 818, 1902.

the toxin. These observations were confirmed by Meyer and Ransom[125] by independent researches. They observed, moreover, that the symptoms of tetanus occurred early if the region inoculated was near the central nervous system, and that the period of incubation was long when the inoculation was remote from the cord, thus showing that the length of the nerve governed the period of incubation, a fact previously emphasized by Courmont and Doyon.[126] Meyer and Ransom, moreover, found the toxin in the axis-cylinders, and ascertained that when it was injected after these structures had been severed, the upper segment did not contain the poison. The latter travelled centripetally and entered the nerve, not by way of the neural capillaries, but by the bare axis-cylinder endings in the muscle. These and other experiments led these investigators to conclude that the toxin did not reach the central nervous system by the lymphatics, but *solely* by the axis-cylinders. They suggested that there must be in these structures "a current of protoplasm" which carried the toxin to the central cells. That the toxin did not penetrate the axis-cylinders by way of the lymphatics had also been demonstrated by Marie and Morax.[127] These investigators suggested that it was "absorbed" by these structures. With the axis-cylinders as plasma-capillaries, we need no tentative theories to explain this process: It is the blood-plasma that enters these minute channels to which Schäfer[128] refers as "extremely fine tubes filled with fluid" which carries the toxin while coursing through them.

The presence of the oxidizing substance, *i.e.*, adrenoxidase, in these nerve-channels suggests itself in view of the facts that the plasma invariably contains this substance, as we have seen, and that it is the albuminous and main component (94 per cent.) of hæmoglobin, which circulates as just shown in the ganglia and nerves of some animals. But direct evidence to this effect is also available. As stated by Barker,[129] "the conditions in the nerve structures essential to methylene-blue reactions" are, according to Ehrlich (1886), "(1) oxygen saturation, (2) alkalinity." As is well known, injections of methylene-blue into animals causes their axis-cylinders, nerve-endings, etc., to become intensely blue, thus proving the presence of considerable oxygen in these structures. Again, since the methylene-blue penetrates the nerves, though injected in the subcutaneous tissues to be absorbed by the blood, it is evident that it is the latter, or rather its oxygen-laden plasma, which carries the stain into the axis-cylinders, nerve-endings, etc.—precisely as is the case with tetanus toxin.

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[125] Meyer and Ransom: Proceedings Royal Soc., vol. lxxii, p. 26, 1904.
[126] Courmont and Doyon: "Le tétanos," Paris, 1899.
[127] Marie and Morax: *Loc. cit.*
[128] *Cf.* vol. i, p. 535.
[129] Barker: N. Y. Med. Jour., May 15, *et seq.*, 1897-98.

That the methylene-blue actually penetrates into the axis-cylinders was recently demonstrated by Meltzer, of New York.[130] Intravenous injections were followed not only by staining of these structures throughout their entire length, but when a segment of nerve was isolated between two ligatures, it failed to be stained, thus showing that the methylene-blue entered the nerve by way of its extremities, central and peripheral. Although chloride of gold and nitrate of silver solutions penetrated the axis-cylinder from the side, at Ranvier's nodes, staining the axis-cylinders a short distance, the methylene-blue solution circulated from end to end. The concurrence with the circulation of tetanus toxin as to the rôle of the axis-cylinders as channels for the methylene-blue stained plasma is self-evident.

Again, as shown by Apáthy, the structures stained with methylene-blue are also stained by his chloride of gold method. This coincides with Meltzer's observation that the axis-cylinders also take both these stains. Now, Barker writes: "Inside the *ganglion-cells* a recticulum of fine fibrils *derived from the neuro-fibrils* in transit can be stained a beautiful deep-violet color by Apáthy's chloride of gold method." This confirms the observation of Adamkiewicz as to the circulation of blood-plasma in the ganglionic cells. It explains also why Meltzer found that the methylene-blue entered the axis-cylinders by way of the central nerve-cells as well as through peripheral nerve-endings. Indeed, that it is the fluid which circulates in the axis-cylinders that is present in the cellular network of neuro-fibrils is further shown by the familiar fact that the latter is also stained by methylene-blue. The link with Meltzer's observation now appears: "Apáthy, Bethe, Nissl and other histologists have all found that the neuro-fibrils which reach the cell-body of a neuron by way of its dendrites passed out of it again to *take part in the formation of the axis-cylinder*—thus entering the latter from above, *i.e.*, by way of the central cell."

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[130] Meltzer: Amer. Jour. of Physiol., vol. x, p. xxiv, 1903-4.

All this points to another fact, viz., that Apáthy's neurofibrils are likewise channels for adrenoxidase-laden blood-plasma, as I suggested in the first volume, for if it is blood-plasma which carries the stains from below, it is the same fluid which carries it from above.

While this affords evidence in favor of the neuro-fibril theory, it does not support Apáthy, Bethe, Nissl and their followers in the belief that this theory overthrows the neuron doctrine now accepted by most neurologists, including Déjerine, Obersteiner and Barker, and histologists such as Kölliker, Ramon y Cajal, van Lenhossek and van Gehuchten, since the neuro-fibrils can no longer be considered as "conductors," as plasma capillaries. Moreover, Ramon y Cajal has shown recently[131] by means of new staining methods, that the ends of the dendrites, *i.e.*, the neuron's protoplasmic extensions, are independent nervous elements with free endings, and that they are varicose, while the neuro-fibrils are smooth. The latter were found to form two close networks, in which the fibrils anastomosed freely, one network extending between the dendrites (Golgi's network), the other sending large fibrils into the cell. In some dendrites large fibrils could be traced to the nucleus, around which they formed a dense perinuclear mass. As these, interpreted from my viewpoint, are all plasma capillaries, the neuron preserves its identity as an independent anatomical structure, just as a kidney remains a kidney though traversed by many blood-vessels, and though its parenchyma contains a multitude of capillaries. The need of these in the formation of the nerve-impulse is shown by the fact that, as stated by Howell,[132] "a nerve placed in an atmosphere free from oxygen loses its irritability, and regains it quickly upon the admission of oxygen." Briefly, we are not dealing, as stated above, with conductors of nerve energy as Apáthy, Bethe and their followers believe, but with *the circulation of the neuron.*

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[131] Ramon y Cajal: Archives latines de méd. et de biol., T. 1, No. 1, Oct. 20, 1903.

[132] Howell: "T. B. of Physiology," p. 113, 1905.

This applies likewise to *nucleo-proteid,* the presence of which in nerve-cells was shown in the preceding section. Interesting in this connection is a remark of Halliburton's brought out by Baumstark,[183] who referred to "the *chief proteid matter* in nervous tissue as resembling casein." "There is a certain amount of truth in this," says Halliburton, "for it is a nucleo-proteid." This is true of brain-cells as well. Levene[184] found that "the nucleo-compound of the brain was a true nucleo-proteid."

Although the presence of *ferments* in nervous tissues has not been determined specifically, it is a necessary factor in the biochemical processes of which nerve-cells and their prolongations, dendrites and axis-cylinders, are known to be the seat. Thus, Halliburton[185] found fresh nervous tissues invariably alkaline; and that on exposure they rapidly became acid. He ascribed this change to lactic acid, stating, however, that Müller and Gschleiden had concluded that it was due to *fermentation* lactic acid. We have a counterpart of this process in the formation of lactic acid in muscles, the sarcolactic acid. The lactic acid formed in milk may also be elaborated, as in muscles, irrespective of any bacterial action. Thus Babcock and Russell[186] found that, notwithstanding the total absence of bacterial influence, insured by careful sterilization, casein was steadily being digested. Their experiments led to the conclusion that this was due to a ferment which they classed among the trypsins. If, now, Baumstark's observation that the "chief proteid matter in nervous tissue" resembles casein, and Halliburton's remark that this casein-like body is nucleo-proteid, are taken into account, and the casein-like nucleo-proteid given the position it occupies in milk as a substance which is being digested by the trypsin (considered elsewhere as a hydrolytic triad), we have evidence to the effect that catabolism is not only a feature of nervous tissue metabolism, but also that it corresponds with that of all other cells. Briefly, I showed in a preceding section,[187] that leucocytes supply nucleo-proteid granules to nerve-cells as well as to other cellular elements; we now find that, as in all other cells, it is nucleo-proteid which is broken down by the action of a ferment.

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[183] Baumstark: Zeit. f. physiol., Chemie, Bd. ix, S. 145, 1885.

[184] Levene: Arch. of Neurol. and Psycho-Path., vol. ii, Nos. 1-2, p. 3, 1899.

[185] Halliburton: *Loc. cit.*, p. 82.

[186] Babcock and Russell: Annual Rep. of Agricul. Exp. Sta., Univ. of Wisc., 1897.

[187] *Cf.* this vol., p. 902 *et seq.*

That nerve-cells must be the seat of metabolism as well as other kinds of cells imposes itself as a logical conclusion. Soury,[138] in his comprehensive treatise, says in this connection: "On the whole, the metabolic processes in the spinal ganglia are most active. Levi[139] found therein a quantity of granules greater than in any other nervous element in the organism. It is evident that the quantity of these intracellular exchange products affords a criterion as to the metabolic activity of a nervous element. Ranvier has pointed out the great vascular wealth of the spinal ganglia of mammals. It is, in fact, probable that not only in the spinal ganglia, but also in *nerve-cells in general*, the metabolic processes are very active." He adduces as evidence to this effect "besides the abundant vascularization of all the centers and nerves of the organism, the fact that of all the elements of the body, the nerve-cell is that which bears the least well a diminution of oxygen."

Cytology and pathology furnish direct evidence in this direction:—

The predominant rôle of chromatin in the vital functions of cells have caused it to be regarded by cytologists as the cellular living substance, that which is being constantly disintegrated and replaced concomitantly by new matter. This applies likewise, as is well known, to the chromatin of nerve-cells. Now, Halliburton,[140] alluding to chromatolysis of the Nissl granules, writes: "It occurs in various abnormal states and under the influence of certain poisons, and its occurrence indicates a diminution of the *vital interaction* between the highly phosphorized nucleus and the surrounding protoplasm. Chromatolysis alone, however, is not indicative of cell destruction, and the cell may recover its functions later when the abnormal condition passes off." It is evidently the nucleo-proteid which is thus reduced, and—as inferred—replaced; for, as stated by the same author with reference to the "fine dust-like particles" into which the granules are reduced, "micro-chemical methods have shown that they consist of nucleo-proteid."

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[138] Soury: "Système nerveux central," Tome ii, Paris, 1899.
[139] Levi: Riv. di patol. nerv. e ment., p. 169 *et seq.*, 1896.
[140] Halliburton: *Loc. cit.*, p. 57.

The nerve-cell differs from the typical cell described by zoölogists in one particular—a feature which assumes a normal aspect in the light of the foregoing evidence, viz., that its nutrition and its reproduction are not solely under the domain of the cell-body, at least in young animals.

"Many experiments have shown," says Verworn,[141] "that protoplasm is incapable of self-preservation without the cell-nucleus, and the nucleus similarly incapable without the protoplasm." If, for example, *Stentor Roeselii*, a trumpet-shaped infusorian, be cut so that one piece will contain protoplasm and nucleus, and the other only protoplasm, "the former continues to live and represents a complete cell, while the other, possessing no longer the individuality of a cell, invariably perishes." As stated by Wilson, the latter ceases to assimilate or grow, and is devoid of the power of repair. This is thought by physiologists to apply to nerve-cells; thus Stewart[142] writes: "Nerve-fibers are 'bound in the bundle of life' with the nerve-cells from which their axis-cylinders arise: the connection between cell and axon once severed, the nerve-fiber dies inevitably." That this can no longer be taken as a guiding-principle, however, is shown by the following facts.

"The question of the possibility of autoregeneration of the distal end of a divided nerve which has been prevented from uniting with its central end is one of great interest," wrote Barker,[143] who also says: "Bethe has repeated the earlier experiments of Philippeaux and Vulpian, and asserts that in young animals autoregeneration takes place, the Schwann cells, uniting end to end, building the new nerve-fibers and producing not only new axons, but actually new myelin sheaths and neurofibrils. Bethe's experiments have been confirmed by Ballance and Stewart in England, van Gehuchten in Belgium, Barfurth[144] in Germany, and recently by Raimann." The facts that, as we have seen, axis-cylinders receive blood-plasma by way of their *peripheral* nerve-endings, and that the nerve-substance, includ-

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[141] Verworn: *Loc. cit.*, p. 60.
[142] Stewart: *Loc. cit.*, p. 605.
[143] Barker: N. Y. Med. Jour., Apr. 7, 1906.
[144] Barfurth: Anat. Anzeiger, Jena, Bd. xxvii, Suppl., S. 160, 1905.

ing the myelin, receives nucleo-proteid granules through the intermediary of leucocytes, readily account for this phenomenon, every nerve-segment, whether above or below the section, being nourished as if it were an ordinary tissue-cell.

Barker remarks, however, that the validity of the experiments referred to above "has been denied by Munzer and by Langley and Anderson,[145] the latter asserting that if anastomosis with other nerves in the limb and all possibility of outgrowth from the central stump be prevented no autoregeneration occurs." In the light of my views these experiments impair in no way the observations of Philippeaux and Vulpian, Bethe and their followers. The process of regeneration being intimately bound up with that of nutrition, the anastomotic branches of the divided nerve may subserve important rôles in this function, both direct and indirect. Under these conditions division of these branches cannot but prevent the reparative process. This applies as well to the prevention of outgrowth from the central stump. If this outgrowth happens to be a feature of the regenerative process, the latter including a simultaneous development of both stumps, artificial prevention of the outgrowth of one of them must inevitably invalidate the process of repair. Interpreted from my standpoint, therefore, the experimental procedures of Munzer and of Langley and Anderson merely rendered the autoregeneration of the divided nerve impossible by impairing the mechanism upon which it depends.

The importance of this feature of the problem lies in the fact that the regeneration of the peripheral stump has been, and is now, regarded, even by the supporters of the neuron theory, as a serious obstacle. In the light of my views, it contributes additional evidence to the effect that a neuron is nourished throughout its entire length, and serves, with other available testimony, to raise the neuron to a higher position than it now occupies, since it emphasizes the fact that it is not merely a cell, but a structure composed of *many cells*, and therefore an *organ*—traversed, like all other organs, by blood channels.

Many investigators, Capobianco and Fragnito, Paladino, Fischer, Hill, Bechterew, van Gieson, Sachs, Nissl and others have urged this view to offset Waldeyer's conception of the neuron as a cell or unit, the tendency being even to drop the term "neuron."[146] I can see no practical advantage in this; Waldeyer's term is so generally accepted that a new term would merely introduce another source of confusion.

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[145] Langley and Anderson: Jour. of Physiol., vol. xxxi, p. 418, 1904.

That a nerve, *including the various structures which constitute a neuron, is built of cells fused end to end, is sustained by considerable evidence.* Apáthy, Bethe, Rosenheim and Benda, Wynn and other histologists hold that the neuro-fibrils are differentiated from these neuroblasts or formative cells, while the rest of the cell becomes a sponge-like reticulum destined to hold the fatty substance (casein-like, to recall a former comparison), the myelin. Many embryologists, including Hertwig, Beard and Balfour, besides Apáthy and Bethe, contend that the peripheral nerves are developed from migrated neuroblasts, the end-result being that described by histologists. Physiology adduces the "avalanche" phenomenon observed by Pflüger, *i.e.*, increase of the intensity of the impulse throughout the length of the nerve, and as the segments increase in number. Durante[147] strongly urges this view, and states that it explains the presence of normal nerve trunks in embryos in which the central nervous system is absent. This author also points out—the contribution of pathology to the question—that during Wallerian degeneration each segment breaks down as a separate entity, and that in peripheral neuritis the lesions may be strictly localized in a single segment. Finally Barker, referring to the recent investigations of Capobianco and Fragnito,[148] Pighini[149] and La Pegna,[150] writes: "This pluricellular or catenary explanation of the origin of the peripheral fibers has been extended even to the dendrites and the nerve-cell of the central organs, certain Italian investigators especially asserting that the rows of cells fuse inside the central system to give rise to them, their nuclei gradually disappearing."

While all this may be said fairly to apply to the formation of myelin-sheaths, the conclusion that the development of the axis-cylinder is also a product of the sheath-cells is only infer-

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[146] Durante: Le bulletin Médical, Aug. 23, p. 732, 1905.
[147] Durante: *Ibid.*, p. 47.
[148] Capobianco and Fragnito: Annali di Neurologia, vol. xvii, 1899.
[149] Pighini: Bibliogr. Anat., Paris and Nancy, T. xvi, p. 74-105.
[150] La Pegna: Annali di Neuroligia, vol. xxii, 1904.

ential. As stated by Böhm, Davidoff and Huber,[181] "the segmental structure of nerve-fibers would seem to give the impression that they are formed by a number of cells fused end to end;" but they refer to their description of the ganglion cells and their processes as showing that "this can be the case only so far as the nerve-sheaths are concerned." All the testimony submitted in this section as to the circulation of the plasma (the freedom with which tetanus toxins ascend to the nerve-cell, the end-to-end circulation of methylene-blue, etc.) in the axis-cylinder points in the same direction. Barker recalls "the embryologic researches of His, which taught that the *axis-cylinder* of a nerve-fiber represents the outgrowth from a single nerve-cell" and that "the studies of Golgi's preparations of young embryos confirmed in the most striking way the opinion of His." He mentions also the recent experiments of R. G. Harrison,[182] which conclusively showed that "naked, non-nucleated fibers which could be traced as such all the way from the spinal cord to the extreme ventral part of the musculature" had developed from the anterior horns "in the entire absence of sheath cells."

As interpreted from my standpoint, these fibers are, of course, plasma channels (the rôle I have ascribed to them as axis-cylinders or neuro-fibrils), and not as Barker calls them "motor-nerves," nor even as Apáthy terms them "conductors." In fact, as is well known, and as Stewart says, the nerve-impulse "passes *over the nerve* with a measurable velocity." Evidence to the effect that the axis-cylinder is not a conductor is also available in Durante's paper—though this observer was not aware, of course, of the identity of the fibers as neural capillaries: "A normal nerve," writes this clinician, "is endowed with two essential physiological properties, *conductibility* (the property of transmitting the nerve-impulse) and *excitability* (that of transforming exogenous vibrations into vibrations capable of being transmitted along nerve-paths). In the course of regeneration, fifteen or twenty days after section and immediate suture of a motor trunk, the voluntary movements recur, although electric excitation of the peripheral end gives no result

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[181] Böhm, Davidhoff and Huber: "T. B. of Histology," p. 160, 1905.

[182] R. G. Harrison: Sitzungsber. d. Niederrhein Gesellsch. Nat. u. Heilk., 1904.

(Duchenne). Then, indirect currents applied upon the central end [the sutured stump] provoke contractions, while no result is obtained by exciting the scar or the peripheral end (Erb). The peripheral end is thus a conductor before being excitable. At this stage, as Howell and Hubert, Weiss, etc., have been able to observe, this peripheral end is still composed of imperfectly differentiated embryonic protoplasmic tubes. These and other facts tend to show that the protoplasm of *neuroblasts*, even when undifferentiated, can *alone* transmit, at least partly, nervous impulses, and this *in the absence of the axis-cylinder* which has been considered as the conductor par excellence."

This evidence, backed by all the data previously adduced, speaks for itself. Referring to the function of the myelin-sheath, Howell[153] states (1905) that "nothing that is certain can be said upon this point." In the first volume[154] I pointed out that it did not act as a mere insulating material as now believed, this rôle being probably fulfilled by the keratin neurilemma, and that it—the myelin, or white substance of Schwann—was the active agency in the elaboration of the nerve-impulse. We now see that the true nervous matter is the product of a chain of neuroblasts which, at a given time, surrounds the axis-cylinder, forming the so-called myelin-sheath, and that it is this structure which, in the absence of the axis-cylinder, transmits nerve-impulses. The "avalanche" phenomenon affording proof that the latter increase in activity with the length of a nerve, it is plain that each neuroblast must contribute nerve energy to the sum total produced. The neuroblast being a segment of the myelin, it follows that I did not err when in 1903 I considered the latter as the source of the nerve-impulse.

The identity of the nerve-cells composing a neuraxon or nerve now suggests itself. The so-called myelin-sheath is subdivided, as is well known, at intervals varying from 80 to 900 μ by constrictions, the nodes of Ranvier, through which the axis-cylinder passes. Each segment thus formed is a *cell* supplied, like all other cells, with a nucleus. This, in the light of my views, is the only true nerve-cell—the cell-body and its dendrites being the sensorium of the whole structure—while the neuron assumes the rank of an organ, just as a sweat-gland is an organ.

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[153] Howell: *Loc. cit.*, p. 72.
[154] *Cf.* vol. I, p. 542.

Briefly, this evidence has served to show (1) *that a neuron is not a cell, but an organ composed of many cells;* (2) *that like all other cells of the body, the cells composing a neuron contain adrenoxidase, nucleo-proteid, and a trypsin-like ferment;* (3) *that the axis-cylinders are the extension in the nerve of the neuro-fibrils which enter the dendrites from above and form a meshwork in the cell-body* (*the main cell of the neuron*) *and around its nucleus;* (4) *that the neuro-fibrils, including the network in the cell-body and the axis-cylinders, are not, as now believed, conductors, but capillaries which supply adrenoxidase-laden plasma to the cells of the neuron;* (5) *that the myelin is not, as now believed, a mere insulating material, but the seat of the metabolic processes to which the formation of nervous energy is due.*

Other phases of the question as a whole must be studied before the process through which the nerve-impulse is produced, and the nature of the impulse, can itself be analyzed.

THE GRANULATIONS OF LEUCOCYTES AS LIVING SUBSTANCE.

The sponge, as we have seen, is to a certain extent a counterpart of the cell-aggregates which constitute many highly differentiated organs, both as to structure and as to the manner in which their existence as living organisms is maintained. Its channels are traversed, as shown by Robert Grant, in 1820, by water currents (propelled by ciliated collar-cells), which enter by minute pores and leave by larger apical apertures. As stated by Professor Minchin,[155] the animal receives in this way "a supply of oxygen for respiration." If we compare these minute afferent pores with the permeable walls of our capillaries and the efferent apertures of the sponge with our lymph-vessels, substituting for the water currents our plasma currents (which become lymph currents in the lymphatic spaces), considerable analogy between the irrigating process of the sponge and that of our tissues will appear. Just as a sponge is "a city of cells," with canals coursing between them, so are our tissues "cities of cells" with canals, our intercellular spaces, the lymph-streams, simply replacing the sea-water streams. Indeed, Loisel[156] has compared the mesoglœa of sponges to lymph. This striking analogy applies even to the porous walls in which the colonies are encased, since our tissue-cells are likewise enclosed in porous connective tissue. A group of sponge-cells may thus be said to exemplify the tissue-cells in one of our lymph spaces. Finally, the excurrent canals, as the analogues of the lymphatic capillaries, serve similarly as a drainage system for these cavities. "By the outgoing current," writes Minchin,[157] referring to sponges in general, "the waste products of metabolism are removed from the body."

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[155] Minchin: Ray Lankester's "Treatise on Zoölogy," Pt. II, 1900.

The manner in which the tissue-cells of these lowly animals are nourished corresponds also—in the light of my views—with that of our own tissues, Fiedler's "Nährzellen," *i.e.*, nourishing-cells or *trophocytes*, being, as their name indicates, recognized by naturalists as food-bearers, while their granules find their counterpart in "excessively minute" cells referred to by Minchin, which "often occur in nests as if they had originated from the breaking up of larger cells," *i.e.*, the wandering cells or leucocytes. That these cells can supply their granulations as nutritive particles, is also rendered evident by the observations of zoölogists. Minchin,[158] referring to the researches of Maas,[159] writes: "In *Spongilla* each ovum becomes surrounded by a follicle formed of the parenchyma, amongst which a certain number of trophocytes work their way. The trophocytes are concerned with the *nutrition* of the ovum. . . . The nutriment received *from the trophocytes* being worked up into *yolk granules*." We will see presently that the nutrition is but a prototype of the mode of nutrition of all cells.

The rôle of these trophocytes exemplifies the general function carried on by leucocytes in the nutrition of cellular elements in the higher organisms, as I interpret it, the parenchymatous follicles representing a "city of cells" in our lymph spaces. The conversion of the nutriment into yolk granules is ascribed by Maas, however, to an intrinsic process in the recipient, *i.e.*, the ovum; but as we have seen, there is ample evidence to show that the leucocytes themselves convert food-stuffs into assimilable end-products, their granulations. Again, I have referred to these cells as "tissue-builders;" even this cardinal function is exemplified by their rôle in the sponge. Professor Minchin, for example, states that "archæocytes," the name given to these wandering cells when they assume the rôle of germ-cells, "are capable of giving rise again as sexual cells, to *the whole organism*, or, in the gemmules, to any form of tissue."

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[156] Loisel: Jour. de l'Anat. et de la Physiol., vol. xxxiv, pp. 1-187, 1898.
[157] Minchin: *Loc. cit.*
[158] Minchin: *Loc. cit.*, p. 61.
[159] Maas: Anat. Anzeiger, Bd. xvi, Nu. 12, S. 290, 1899.

The function that leucocytes can fulfill in this connection, *i.e.*, as tissue-builders and germ-cells, is of far-reaching importance. It affords (1) a clue to the manner in which the leucocyte granulations penetrate tissue-cells to carry on their functions therein, and (2) proof that they—the leucocyte granulations—are living organisms in the sense that spermatozoa are living cells.

A spermatozoön, in fact, differs but little from a leucocyte granulation. "The head of the spermatozoön represents the nucleus," writes Howell,[160] "and contains the valuable chromatin material." We have seen that the phosphorus-laden nuclein is the active agent of the granulations. The same physiologist says:[161] "These heads consist entirely of nuclear material." . . . "Miescher, in investigations upon the spermatozoa of salmon, discovered that the heads are composed essentially of an organic combination of phosphoric acid, since designated as nucleic acid, united with a basic albuminous body, protamin. This view has been confirmed and extended by later observers, especially Kossel and his pupils."[162] Inasmuch as protamin is a proteid, the head of a spermatozoön may be said to be composed, like a leucocyte granulation, of nucleoproteid. Again, as likewise shown by Kossel, the quantity of alloxuric bases is considerable only in blood rich in leucocytes. "In such blood," says Hammarsten,[163] "Kossel found 1.04 per mille nuclein bases against only traces in the normal blood." Now, Howell, alluding to the nucleic acid in the spermatozoa of the salmon, states that "on decomposition by hydrolysis it yields at first some of the purin bases (adenin, guanin) . . " etc. Even the minuteness of the leucocyte granulation is a known characteristic of the head of the spermatozoon.

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[160] Howell: *Loc. cit.*, p. 850.
[161] Howell: *Loc. cit.*, p. 862.
[162] Burian: Ergebnisse der Physiol., Bd III, Hft. 1, 1904.
[163] Hammarsten: *Loc. cit.*, p. 131.

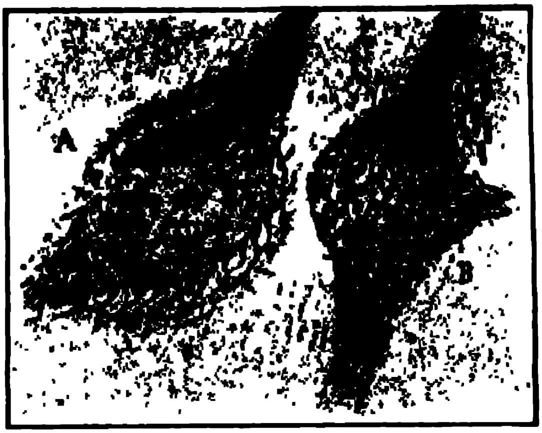
The analogy between the head of the spermatozoön and the leucocytic granulation as to their biochemistry is especially striking. It extends also to the motility of the organisms. As observed by Stokes and Wegefarth, Sangree, Gulland, Bell and [illegible] the granulations actually leave the leucocyte and show considerable agitation. Sangree[illegible] saw fifty or sixty granulations leave a leucocyte at a time, with considerable velocity; some moving away oscillating while others in masses "would move in one direction, wave this way and that, and finally return to the central body"—the cell.

Stokes and Wegefarth write to illustrate their motility of these granulations, when exposed to a temperature approximating that of the body: "At times the granular leucocytes become actively amœboid, and the granules *within* the neutrophile exhibit a characteristic activity which might be compared to the swarming of bees around a hive. The number of fine granules free in the plasma is perceptibly increased. The eosinophilic granulations also show a less vigorous tremulous motion, and both varieties follow the changes in the direction of the pseudopodia, the protoplasm being thrown out first, and the granules following. The characteristic dancing motion of the granules in the neutrophilic leucocyte can be brought out very plainly by simply mixing the drop of blood with an equal amount of distilled water containing 1 per cent. of alcohol. The granules become very active and present a characteristic picture."

The granulations of leucocytes are thus similar to spermatozoa in chemical composition, staining properties; like these organisms they are motile—the motions in both being vibratile—and they are capable of becoming chromosomes in the process of reproduction. They are practically tailless spermatozoa such as those of myriapods, and when "they work their way" into the tissues, and enter cells in aggregated masses (as in the cell-body of neurons), recall the spermatophores of certain urodeles. The penetration of the granulations into tissue-cells thus becomes a normal feature of the process of nutrition; they enter the cell as a spermatozoön enters an ovum. In my opinion Auerbach's "terminal buttons" are naught else than such granulations, as shown in the annexed plate.

[illegible] Cf. this vol., p. [illegible].

[illegible] Sangree: Medical Bulletin, Jan., [illegible].



LEUCOCYTE GRANULATIONS IN THE ACT OF PENETRATING THE CELL-BODY OF A NEURON. *(Sajous.)*

Now regarded as the "terminal button of Auerbach." Two large funicular cells of the spinal cord of the adult rabbit. After Ramon y Cajal, 1903.

(*Barker.*)

That they are *living bodies* is another conclusion imposed by their correspondence with spermatozoa, which are themselves regarded as living cells. Landois,[166] for example, writes that "the spermatozoa of the frog may be frozen four times successively without injury; they endure a heat of 43.75° C. and continue to *live* for seventy days in the testicle transplanted to the abdominal cavity of another frog." Now, we have seen that the head of the spermatozoön contains chromatin and also that all cells show among the granules in their protoplasm some that correspond in their staining properties and chemical composition with those of leucocyte granulations.

If, however, these granulations are living structures, the cellular chromatic granules should also be endowed with life. Henle (1841), and subsequently Béchamp and Estor, Maggi and Altmann held that "*microsomes* are actually organic units or bioblasts capable of assimilation, growth and division, and hence to be regarded as elementary units of structure standing between the cell and the ultimate molecules of living matter.[167] Altmann's conception,[168] the most comprehensive, was that a cell was a colony of such elementary granules or "bioblasts" capable of leading an independent existence. Bacteria, for instance, were considered as "bioblasts;" so were waste-products, oil-droplets, and many other heterogeneous substances. Such a widespread application of the theory caused it naturally to be received with great skepticism, and practically to be set aside when bacteria were found to be cells. As shown below, however, there is good ground for the view that the microsomes of a cell are living entities. Indeed, it is possible also that leucocyte granulations may prove to be cells in keeping with spermatozoa. Minchin, for example, refers to the granules derived from the trophocytes of sponges as "excessively minute cells" having "a nucleus and a clear cytoplasm." Müller[169] also alludes to markedly active granules found in lymph "enclosed in an albuminoid covering."

Many other investigators, as previously stated, have based comprehensive theories on the presence in all cells of living or viable units. The "physiological units" of Herbert Spencer, to which this great philosopher ascribed the phenomena of regeneration, development and heredity, Weismann's "biophores," Beale's "bioblasts," Verworn's "biogens," and the various hypothetical units of cellular organization and function introduced in the writings of Darwin, de Vries, Haeckel, Foster and other authorities, certainly point to the need of such elementary bodies to account for vital phenomena. Indeed, Verworn refers[170] to his "biogens" as "the real bearers of life," hence to living units.

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[166] Landois: "T. B. of Human Physiology," Amer. edition, p. 945, 1905.

[167] Wilson: *Loc. cit.*, p. 21.

[168] Altmann: Archiv f. Anat. u. Physiol., Physiol. Abth., S. 524, 1889.

[169] Müller cited by Berdal, "Histologie normale," Paris, 1894.

Again, Wilson, after reviewing some of the foregoing evidence, and referring to cells in general, writes: "Many of the granules, especially the larger and more obvious of them, are unquestionably inert bodies, such as reserve food-matters, suspended in the meshwork. Others are the nodes of the network or optical sections of the threads. But there is some reason to believe that, apart from these appearances, discrete *living* particles may form a constant and essential feature of the protoplasmic thread. These particles, now generally known as *microsomes* (Hanstein, '82), are embedded in threads of the network." The latter does not alone embody the living constituents of the cell, for he says, elsewhere,[171] after reviewing the labors of Van Beneden, Heidenhain, Reinke and Schloter: "When all these facts are placed in connection, we find it difficult to escape the conclusion that no definite line can be drawn between the *cytoplasmic microsomes* at one extreme and the *chromatin* granules at the other. And inasmuch as the latter are certainly capable of growth and division, we cannot deny the possibility that the former may have like powers."

This conclusion harmonizes with my own reached from a different direction, both as to the functional relationship of the nutritional leucocyte with the tissue-cell, and as to the kinship of its granulations with the biochemical structure of the spermatozoön and its rôle in reproduction. Just as the germ-cell is a living unit, so is the chromatin granule or microsome a living unit, and the leucocyte granulation, being naught else than a chromatin granule when transferred to the tissue-cell, is likewise, therefore, a living unit. So close a kinship between the spermatozoön and the leucocyte granulation appears anomalous; but we must not overlook the fact that, interpreted from my standpoint, the granulation perpetuates, as nutritional substance, what the spermatozoön initiates, *i.e.*, the life process.

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[170] Verworn: *Loc. cit.*, p. 484.
[171] Wilson: *Loc. cit.*, p. 222.

This evidence appears to me to warrant the following conclusions: (1) *that the granulations of leucocytes are living units which perpetuate in the organism what the spermatozoa initiate in the ova, viz., the vital process, the cellular development;* (2) *that when leucocytes migrate from the blood to the tissue-cells in the lymph spaces, the granulations they secrete therein penetrate into the cells as spermatozoa penetrate into the ova;* and (3) *that the granulations of nutritional leucocytes become the nucleo-proteid chromatin granules or microsomes of tissue-cells.*

THE ACTIVE PRINCIPLE OF ADRENOXIDASE AS THE DYNAMIC ELEMENT OF LIFE.

The leucocytes, as we have seen, supply granulations to the tissue-cells and constitute their chromatin granules. An important discrimination becomes necessary in this connection, however. Wilson, referring to the investigations of Heidenhain, confirmed by Reinke and Schloter, states that "the nuclear network contains granules of two kinds, differing in their staining capacity. The first are *basi*chromatin granules, which stain with true *nuclear* dyes (basic anilines) and are identical with the 'chromatin granules' of other authors. The second are the *oxy*chromatin granules of the *linin* network, which stain with *plasma* stains (acid anilines, etc.), and are closely similar to those of the cytoreticulum" or network. The first are evidently the nucleo-proteid granules derived from leucocytes, since Heidenhain found, in accord with other physiological chemists, that "basichromatin is a substance rich in phosphorus (*i.e.*, nucleic acid)." The identity of oxychromatin is as self-evident, but its importance in the vital process is so great that I will submit, along with the data which indicate the rôle of oxychromatin, testimony to the effect that this substance is adrenoxidase.

Huxley's definition of life: "A universal *disintegration* and waste of oxidation, and its concomitant *reintegration* by the intussusception of new matter," depicts the sequence of events in cellular metabolism. This conception involves first of all the breaking down of worn, though still living substance, and its replacement by materials derived from the exterior, but evidently capable only of *acquiring* life. As Spencer says: "No separate molecule of proteid possesses vitality."

The manner in which the first part of the process, the disintegration of living matter, is brought about, is suggested in the following lines by Chittenden: "Chemical study has shown that nucleo-proteids, by simple *hydrolysis* with mineral acids in a flask, can be broken down in some form of proteid, phosphoric acid and one or more purin bases, such as adenin, guanin, xanthin and hypoxanthin . . . . Too much stress cannot be laid upon the easy convertibility of the free purin bases, adenin, guanin, hypoxanthin and xanthin into uric acid *by virtue of the action of the intracellular enzymes* present in so many of the organs and tissues." This undoubtedly applies to chromatin disintegration, for, as stated by Halliburton,[172] Hoppe-Seyler found that the true nucleins, those found in the cell nuclei, yield "proteid xanthin and alloxuric bases" and "phosphoric acid," and that the nuclei "richest in nucleic acid occur in the chromatic fibers of the nucleus."

In the light of these facts it is evident that "disintegration and waste by *oxidation*," as expressed by Huxley, no longer represents the process through which the *living portion* of the cell is destroyed, according to the more advanced teachings of physiological chemistry. Indeed, as we have seen in the preceding chapters,[173] catabolism is not attended by cellular combustion, but by *hydrolytic cleavage*.

Again, Gautier,[174] who pointed out as far back as 1881, that cellular metabolism occurred without the direct participation of oxygen, as in the case of anaerobic bacteria, also attributed the disintegration of the living substance to hydrolytic cleavage. He writes, however, referring to the cell: "It is at the expense of *its products* that the phenomena that furnish the animal the major part of its heat and energy occur." As interpreted from my standpoint, it is not at the expense of its

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[172] Halliburton: Schäfer's "T. B. of Physiol.," vol. i, p. 66, 1898.

[173] *Cf.* this vol., chapters xiii and xiv.

[174] Gautier: "La cellule vivante," Paris, 1881.

products that this bulk of heat energy is liberated. Indeed, the prevailing doctrine does not enlighten us as to the manner in which this energy is produced. "If heat is indispensable to living beings," says Morat, of Lyons,[175] "if the animal has framed, as it were, all its evolutional development so as to regulate it at a fixed and invariable rate; if it spends combustible materials in such quantities to uphold it to a certain level when there is no danger of losing it; and if it wastes and rids itself of it so actively when threatened with an excess of it, heat must be endowed with some rôle of the very first order and absolutely general in its bearing upon the *elementary reactions which sustain life,* while giving the latter its maximal activity and value. It is this rôle that we cannot discern, not even properly define. We are reduced to the realization that such a degree of heat is useful; that another is bearable and that another is harmful, but we cannot give the reasons for this."

Still, Morat touches the keynote of the true process—in the light of my views—when he adds: "It seems, however, that we can connect this factor with the conception, still so vague, of *fermentation.* Fermentation is the paramount chemical process of the living being; fermentation characterizes life; *Life is a fermentation!*"* It is not to hydrolytic cleavage, due to the action of trypsin, however, that Professor Morat refers. After defining the properties of catalytic agents, he writes: "The ferment is thus endowed with the most general characteristic of living beings: it modifies its environment in a specific way without disappearing itself, that is to say, while preserving itself." The final purpose of this catalytic ferment in the vital process is then brought forth in the sentence: "In doing so, it awakens thermogenic reactions."

Yet, how does a catalytic ferment awaken these heat-producing reactions? Obscurity recurs in this connection. The author ascribes the intracellular process to the fact that "*some* agent is capable of converting some such commonplace energy as heat into modalities of energy commensurate with the reaction to be obtained." This is the characteristic effect of the ferment, but the main feature of the problem is left unsolved.

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* The italics are Prof. Morat's own.

[175] Morat: Morat and Doyon, "Traité de Physiologie," Paris, 1899.

Indeed, Morat states that "this enlightens us in no way upon the intimate mechanism of its action."

The identity of the agent that is capable of carrying on these functions suggests itself in the light of all the evidence I have submitted, namely, adrenoxidase. We have seen: (1) that its active principle, that of adrenal secretion, is not only a ferment, but the "ferment of ferments" and, therefore, a component of all cells; (2) that it acts as a catalytic agent or "oxygen transmitter" in all animals provided with adrenals, and that its analogue in animals which are not known to possess such organs, and in plants likewise, acts as a catalytic, and finally, (3) that it acts as a thermogenic agent when its loose oxygen is brought into contact with the phosphorus of nucleo-proteid granules.

Adrenoxidase thus meets all the conditions expressed by the word "fermentation" as Morat—voicing the trend of modern research—interprets it. It follows, therefore, that since, as he says, "Life is a fermentation," *adrenoxidase is the dynamic agent in the vital process.*

What function does adrenoxidase fulfill in the cell?

Pfeffer[176] writes: "Various post-mortem *oxidations* may occur after death, as for example when the *sap* of *Monotropa, Vicia faba,* etc., turns brown. These appear to be produced by the action of certain substances to which the provisional name of *oxydases* may be given." Gautier,[177] alluding to this sap, states that "it is always *acid,* while the protoplasmic portion is always slightly alkaline." He also says that it contains, besides acids, various "products of the cell," including, among other substances, pigments, extractives, sugars, fats, and alkaloids, which "the protoplasmic pockets," *i.e.,* the vacuoles, "could be *seen* in certain instances" to eliminate. Now, the animal cell is similarly supplied with excretory channels. Böhm, Davidoff and Huber state,[178] for example, that among the various structures that protoplasm contains "the vacuoles deserve special mention. They are more or less sharply defined cavities filled with fluid," add these histologists, "and vary considerably in number and size. The fluids that they contain differ somewhat, but are always secreted by the protoplasm, and are, as a rule, finally emptied out of the cell." It is plain that the products thus eliminated are wastes—the identical wastes or decomposition products which, we have seen, it is one of the functions of the lymph to sweep away. In fact, the fluid secreted by the cell evidently corresponds with lymph, since no fluid other than this is derived from cellular elements. Again, the presence of oxidase in the lymph of plants affords additional proof that we are dealing with lymph, since we know that our tissue-cells are bathed in blood-plasma, which invariably, we have seen, contains adrenoxidase, derived from the adjoining capillaries.

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[176] Pfeffer: "Physiology of Plants," vol. 1, p. 545, 1900.
[177] Gautier: *Loc. cit.*, p. 17.
[178] Böhm, Davidoff and Huber: *Loc. cit.*, p. 61, 1905.

An important feature of the question in point asserts itself in this connection: "The plasma of the blood," writes Howell,[179] "makes its way through the thin walls of the capillaries, and is thus brought into *immediate contact* with the tissues, to which it brings . . . . *oxygen* of the blood and from which it removes the waste products of metabolism." In other words, according to the present (1905) teachings, it is the oxygen of the plasma that is supplied to the tissue-cells, and the plasma itself, which has become lymph, merely "bathes" the exterior of the cells, sweeping off the wastes it eliminates. As stated by Landois,[180] however, "It can be conceived that, through contraction and diminution in size of their cell bodies . . . . they [the cells] might exert suction upon the blood-plasma transuded. If the cells, themselves, then take up the transuded fluid, the conception is permissible, further, that by subsequent contraction they express this fluid in a certain direction, namely, from secretory space to secretory space, toward the lymph-capillaries."

This suggestion harmonizes perfectly with the facts embodied in the preceding paragraph. Indeed, the data I have submitted in the foregoing pages indicate (1) that it is not around the tissue-cells that the blood-plasma passes, but *through* these cells, and (2) that they do not absorb oxygen from the plasma, but that the intrinsic cellular process involves the ac-

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[179] Howell: *Loc. cit.*, p. 427.
[180] Landois: *Loc. cit.*, p. 262.

tive participation of the adrenoxidase which passes through the cells with the plasma.

This accounts for the fact that oxidase is present in the fluid eliminated by way of the vacuoles, the cellular emunctories, and for the observation of Abelous and Biarnès[181] *that tissues are even richer in oxidase than the blood itself.* Lillie[182] found, moreover, that animal cells were endowed with oxidizing properties and that lymphocytes and leucocytes contained oxidase. Again, if, as I have pointed out, axis-cylinders and neuro-fibrils contain this substance—adrenoxidase—and that it is on this account that they take methylene-blue, the ground-substance or cytoplasm of cells should also take this stain. Gulland,[183] in an illustrated study of the granular leucocytes, shows several methylene-blue stained cells, in which the cytoplasm, along with other structures to be described presently, took the stain. It is evident, therefore, that the cells absorb the adrenoxidase-laden plasma as it enters the lymph-spaces, and that they eliminate it—probably by contracting periodically—with all wastes, by way of their vacuoles.

The framework of the cell, the *cytoreticulum,* was called by Leydig its "spongioplasm," so greatly did it recall that of the sponge. Referring to this structure, Wilson[184] states that "it is composed of irregular rows of distinct granules which stain intensely blue with hæmatoxylin, while the substance in which they are imbedded, left unstained by hæmatoxylin, is colored by red acid aniline dyes, such as Congo red or acid fuchsin." Elsewhere, in describing a diagram[185] of a cell, he says that "its basis consists of a thread-work (mitome or reticulum) composed of minute granules (microsomes) and traversing a transparent ground-substance." Again,[186] recalling the researches of Van Beneden and his own, he writes: "It is certain that the microsomes are not merely nodes of the network, or optical sections of the thread, as the earlier authors maintained."

What is the nature of these microsomes?

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[181] Abelous and Biarnès: *Loc. cit.*
[182] Lillie: Amer. Jour. of Physiol., vol. vii, p. 412, 1902.
[183] Gulland: Jour. of Physiol., vol. xix, p. 27, 1895-96.
[184] Wilson: *Loc. cit.*, p. 212.
[185] Wilson: *Loc. cit.*, p. 14.
[186] Wilson: *Loc. cit.*, p. 212.

The network of the nucleus contains, as previously stated, basichromatin granules and oxychromatin granules. Again, Wilson refers to the latter as "closely similar to those of the cytoreticulum" or cellular network in their staining properties. As basichromatin granules were found by Heidenhain and others to be rich in phosphorus, those of nuclear network are doubtless composed of nuclein or nucleo-proteid. The nuclear network which corresponds tinctorially with the network of the ground-substance or cytoreticulum, therefore, is that composed of oxychromatin granules. Having now seen that the plasma passes through the cells and that oxidase is present in the fluid eliminated by the cell, there is good ground for the belief that the oxychromatin granules are in reality composed of adrenoxidase. That such is the case is shown by the fact that both substances correspond in their staining properties. Thus, in the leucocytes stained with methylene-blue by Gulland, the cytoreticulum took the stain as well as the cytoplasm, but more intensely. This shows that adrenoxidase is present in both structures though in a more condensed form in the network. Again, Wilson states that the *oxychromatin* network stains with "plasma stains (acid anilines, etc.)," and refers to the fact that the Biondi-Ehrlich mixture of acid fuchsin and methyl-green stains the cytoplasm of leucocytes red. Now, Heidenhain showed that the oxychromatin granules are also stained red by this mixture. Thus, the cytoplasm and the cytoreticulum correspond in their reaction to this stain as they did to methylene-blue. Gulland's plates show the same correspondence with the Biondi-Ehrlich mixture. This is further sustained by the fact that the nucleo-proteid chromatin is stained green by this mixture. Thus Wilson says that the green substance is the "chromatin of Flemming," the basichromatin, which, as stated above, is rich in phosphorus. It is evident, therefore, that *just as the substance in the axis-cylinders of nerves is adrenoxidase* (a fact controlled by the circulation of tetanotoxin-laden plasma in them), *so is the cytoreticulum or spongioplasm of cells composed of adrenoxidase.*

The far-reaching meaning of this conclusion asserts itself in view of the fact that it is a living portion of the cell. "Since I saw the reticulum in *continuous movement* during the life of a protoplasmic lump," says Heitzmann,[187] referring to observations made by him in 1873, on the leucocyte of the newt, "my conclusion was that the reticulum is made up of the living or contractile matter proper; whereas the meshes contained a liquid, destitute as such of properties of life, filling the meshes of the sponge-like structure, and permitting the contraction of the solid portion—*i.e.*, the living matter." More recently, Wilson also wrote,[188] alluding to the "sponge-like network," "At the present time it seems probable that the more solid portion is the more active and is perhaps to be identified as the *living substance proper*, the ground-substance [the cytoplasm] being passive." The rôle I attribute to adrenoxidase, *viz.*, that it is "the dynamic agent in the vital process," harmonizes clearly with this view, especially when we consider that it is probably in its original form that it occurs in the network.

That the "granules" described are formed only after death of the cell, and owing to the methods of fixation employed, is probable, however. We have seen that in its original state—as the albuminous portion of oxyhæmoglobin—adrenoxidase leaves the red corpuscles in the form of droplets, the so-called "blood-platelets" or "hæmatoblasts." Indeed, Löwit[189] found blood-platelets "within capillary blood-vessels just removed from animals, and in which the blood was still fluid," though none could be discovered in the circulating blood. These vessels being the very ones that supply plasma to the lymph spaces, the adrenoxidase droplets reach the cells almost at once after traversing the capillary walls.*

In the preceding section, I pointed out that the granulations of leucocytes were living substance and that they entered the cells as spermatozoa penetrate ova. We have now seen that adrenoxidase is the dynamic agent in the vital process. It is therefore owing to the presence of adrenoxidase in the leucocytes[191] that the nucleo-proteid granulations become living entities. We also find adrenoxidase forming a delicate and close network throughout the cell—a network recognized as the living portion of the cell.

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* The semifluid nature of adrenoxidase suggests that the network or cyticulum is made up of delicate capillaries, or minute tubes or canals such as axis-cylinders are thought to be by Schäfer and others. In the first volume[190] I submitted reasons which had led me to conclude, referring to leucocytes, that "the intracellular and intranuclear network of fibers in mature leucocytes are canaliculi for blood-plasma and for the substances contained in this fluid," and to compare them to neuro-fibrils. As the conclusions of the first volume were intended as suggestions, while the second volume contains only what appears to me fully sustained by available evidence, I will adhere for the time being to the prevailing view that the network is made up only of granular threads, *i.e.*, strings of granules in close apposition.—S.

[187] Heitzmann: Jour. of the N. Y. Micros. Soc., July, p. 66, 1893.

[188] Wilson: *Loc. cit.*, p. 17.

[189] Löwit: Archiv f. exp. Path. u. Pharm., Bd. xxiv, S. 188, 1887.

[190] *Cf.* vol. i, p. 663.

On the whole, the evidence submitted appears to me to warrant the following conclusions: (1) *that adrenoxidase, owing to its ability to act simultaneously: as a catalytic, as oxidizing body, and as the ferment of all ferments, is a dynamic agent in the vital process;* (2) *that the nucleo-proteid granules are evolved as living units by the digestive leucocytes because these cells contain adrenoxidase;* (3) *that the blood-plasma does not, as now believed, on penetrating the lymph-spaces circumvent the tissue-cells and yield its oxygen to them;* (4) *that the blood-plasma on entering the lymph-spaces at once enters the cells and thus supplies them directly with adrenoxidase;* (5) *that the "oxychromatin" network of the nucleus and of the cytoplasm or ground-substance, are both composed of adrenoxidase;* and (6) *that these networks are the living portion of the cell.*

What is the functional relationship between adrenoxidase forming the cellular networks and the nucleo-proteid granules of the cytoplasm?

THE ACTIVE PRINCIPLE OF ADRENOXIDASE AS THE DYNAMIC ELEMENT OF LIFE (continued).

An important constituent of the cell has so far received but little attention. I have repeatedly referred to the function of the nucleo-proteid, but only to that of its phosphorus-laden constituent, the nuclein. Its proteid moiety plays, none the less, a prominent rôle in the vital process; indeed, when the granulations of leucocytes were referred to as living entities in a preceding section, a more detailed analysis of the question—inappropriate at the time—would have pointed to this moiety as a living substance. Thus, Verworn[192] says that "it is the proteids whose presence constitutes the general essential condition and *focus* of life." This estimate is fully sustained when the vital process is interpreted from my standpoint, since the functions I have attributed to nuclein and adrenoxidase had all the same general trend, *viz.*, to convert the dead proteid molecule received as food, into living proteid; to maintain its life *as long as it was useful to the cell; to break it down when worn and convert it into eliminable waste-products.* In brief, the proteid molecule is that *acted upon* in all phases of the vital cycle and essentially, therefore, the focus of vital activity.*

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[191] *Cf.* this vol., p. 894.
[192] Verworn: *Loc. cit.*, p. 480.

The supply of proteid corresponds quantitatively, of course, with that of the nucleo-proteid granules. There is a suggestive contrast, however, between the nucleus and the rest of the cell, "the former," as stated by Wilson,[193] being characterized by an abundance of nuclein, while the cell-body "is especially rich in proteids and related substances (nucleo-albumins, albumins, globulins and others)." The predilection of the nucleus for a substance "rich in phosphorus" such as nuclein is accounted for by the nature of its function. As pointed out by Claude Bernard, it is "an apparatus for organic synthesis, an instrument calculated to produce, and is the germ of the cell." It receives materials, therefore, and adjusts their components to the needs of the latter.

The evidence so far adduced provides only for a promiscuous distribution to the cell in general of leucocyte granulations and adrenoxidase. How does the nucleus acquire its surplus of nuclein?

That nuclei are mobile in the cell-body has been noted by various investigators. Korschelt observed, moreover, that "there is a definite correlation, on the one hand, between the *position* of the nucleus and the *source* of food supply, on the other hand between the size of the nucleus and the extent of its surface and the elaboration of material by the cell," meaning by the latter its secretory activity. He gives as examples the silk-glands of various lepidopterous larvæ (Meckel, Zaddach, etc.). "Here," writes Wilson,[194] who cites Korschelt, "the nucleus forms a labyrinthine network by which its surface is brought to a maximum, pointing to an *active exchange* of material between *nucleus* and *cytoplasm*." Again, "in many of the insects," examples of which are given, "the egg-nucleus at first occupies a central position, but as the egg begins to grow, it moves to the periphery on the side turned toward the nutritive cell." By the latter is meant the "*nurse-cell*" which accompanies developing ova in various insects, including certain butterflies, worms, ear-wigs, etc. The nutriment is evidently transferred from the nutritive cell to that nourished, and in the form of granules. Thus, Wilson writes, referring to the eggs of the water-beetle *Dysticus*, in which Korschelt was able to observe the movements and changes of form in the living object: "The eggs here lie in a single series alternating with chambers of nutritive cells. The latter contain granules which are believed by Korschelt to pass *into the egg*, perhaps bodily, perhaps by dissolving and entering in a liquid form. At all events, the egg contains accumulations of *similar granules* which extend inwards in dense masses from the nutritive cells to the germinal vesicle, which they may more or less completely surround." . . . . "The granules could not be traced into the nucleus, but the latter grows rapidly during these changes, proving," says Wilson, "that matter must be absorbed by it, probably in liquid form."

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* The meaning of "proteid," in the light of my views, is that usually attributed to the common proteids, *i.e.*, those that contain carbon, hydrogen, nitrogen, oxygen and sulphur. Although globulins are classed among proteids, because they give some of the reactions peculiar to the latter, their function differs totally from that of common proteid in the cell, including as they do adrenoxidase. Even more confusing, from my standpoint, is to include nucleoproteid among the proteids, since its nuclein, as do its proteid and adrenoxidase, fulfils an autonomous rôle. The fact also that plasmatic albumins do not, as now believed, supply nutrient materials to the cells—a rôle that I attribute entirely to leucocyte granulations—also imposes the need of a new classification of proteids, since the plasmatic proteids—fibrinogen, for instance—apart from the globulins, are concerned only with the blood's intrinsic functions, coagulation, the maintenance of its own heat, etc.—S.

[193] Wilson: *Loc. cit.*, p. 17.

This affords tangible evidence in several directions, (1) that a cell may be nourished by another, and, therefore, that leucocytes can serve as nurse-cells—as they do, we have seen, in *Spongilla;* (2) that the food may be transferred in the form of granules, some, perhaps, in liquid form; (3) that a nucleus is a mobile structure; (4) that it adjusts its position to the source of the food supply; (5) that it is able as an autonomous body to ingest materials suitable for its own nutrition and growth; and (6) that it can transfer materials to the cytoplasm.

The manner in which the nucleus acquires its abundance of nuclein now suggests itself: The nucleus moves wherever granules derived from leucocytes are most prolific, and when supplied according to its needs, it moves away. Thus, Haberlandt[195] noted that in plants, growth in any part of a cell was always preceded by "a movement of the nucleus to the point of growth," and that after the process was terminated "the nucleus often moves into another part of the cell." That granules may thus enter the nucleus is shown by the fact that bacteria may be drawn into the nucleus of phagocytes as observed by Bail.[196] The same mechanism applies to the adrenoxidase, *i.e.*, the oxychromatin, which, as shown by Heidenhain and others, is also present in the nucleus. Here, the nucleus has merely to move in the part of the cell nearest the capillary from which the latter receives its blood-plasma, to receive, if its functions require it, an unusual supply of adrenoxidase droplets, which, as we have seen, are to be found in the pericellular capillaries.

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[194] Wilson: *Loc. cit.*, p. 254.

There is evidently a close functional relationship between the nucleus and the cytoplasm. When a portion of the latter is cut off from the part of the cell containing the nucleus, it may live for a while and move about normally; but, as Wilson says: "Such a mass of protoplasm is, however, devoid of powers of assimilation, growth and repair, and sooner or later, dies." Inasmuch as we have seen in the preceding section that the cytoplasm contained a close network regarded by many investigators as the *living* portion of the cell, it follows that it must be the nucleus which supplies the cell with its *papulum vitæ*. This is sustained by the fact that, as also shown, the network of cytoreticulum is composed of adrenoxidase droplets. It is evidently this substance which the nucleus deals out to the cytoplasm according to its needs.

The manner in which it does so was analyzed in the first volume.[197] I suggested therein that the so-called "nuclear membrane" was in reality a cavity that contained the substance which, though derived from the nucleus, was projected into the body of the cell, and formed its network, its staining properties (iron-hæmatoxylin) being similar to those of the network. Although the function of this "membrane" has remained unknown, the data recorded sustain my interpretation.

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[195] Haberlandt: Cited by Wilson, *loc. cit.*, p. 262.
[196] Bail: Berl. klin. Woch., Oct. 11, S. 887, 1907.
[197] *Cf.* vol. i, p. 654.

Thus, both Klein and Van Beneden consider it as similar in structure to the network, while Reinke[198] found that it consisted of "oxychromatin granules like those of the linin network"—a nuclear structure. As oxychromatin is adrenoxidase, the nuclear linin, the "nuclear membrane" and the network of the cytoplasm are all composed of adrenoxidase. This is further confirmed by the fact that in Gulland's plate[199] all three structures are shown to have taken methylene-blue. The rôle of the nucleus in the process now seems clear: It utilizes what adrenoxidase it requires for its own use and feeds the rest into the "nuclear membrane"—the perinuclear vacuole, as I have termed it—whence it is projected into the cytoplasm to form the network. Each thread of this network, according to Van Beneden, Wilson and others, is composed "of a single series of microsomes, like a string of beads." As Hammarsten[200] refers to blood-platelets as "pale, colorless, gummy disks," it could be considered as a string of adrenoxidase disks.

Although the network of the cytoplasm is a living structure, its identity as adrenoxidase accounts only in part for this fact, since its properties, those of a catalytic and oxidizing substance, become manifest, in their relation to the vital process, only when nucleo-proteid is present. Since, as we have seen, nucleo-proteid granulations penetrate directly into the cytoplasm, this feature is also met. Still, how are the adrenoxidase droplets of the network and the nucleo-proteid granules of the cytoplasm brought into contact?

We have repeatedly seen that their mutual affinity is very great. So marked is it, in fact, that the blood-plates have been found combined with nuclein in shed blood. Indeed, they jointly subserve two important functions in this fluid as I have pointed out in the first volume:[201] the maintenance of the blood's temperature to its physiological needs; and fibrin coagulation, adrenoxidase being, we have seen, the fibrin-ferment. During life the blood-platelets and the nucleo-proteid granules are dealt out by their respective cells, the red corpuscles and the leucocytes, as needed by the blood and are promptly dissolved. After death, however, or in shed blood, this stage is not reached and the platelets are found either in their normal state (Bizzorero, Hayem, etc.), or in combination with nuclein (Kossel, Lilienfeld, etc.), and called, therefore, "nuclein plates," the latter, though abnormal entities, standing as proof of the mutual affinity of their components. This explains the presence of the close-meshed network in the cytoplasm and also its vital activity, since the affinity of its adrenoxidase for nucleo-proteid causes the granules of the latter to be drawn to the network at once on reaching the periphery of the cell.

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[198] Reinke: Cited by Wilson, *Loc. cit.*, p. 28.
[199] Gulland: *Loc. cit.*
[200] Hammarsten: *Loc. cit.*, p. 186.
[201] *Cf.* vol. i, p. 683 *et seq.*, in the first three editions.

Various phenomena that have remained unexplained now appear as normal consequences of the presence of these two bodies in the cell, both nucleus and cytoplasm. Alluding to the labors of van Beneden, Heidenhain, Reinke and Schloter and to his own investigations, Wilson writes[202] in respect to the two kinds of granules: "These two forms graduate into one another." Referring to the nucleus he says: "The chromatic substance is known to undergo very great changes in staining capacity at different periods in the life of the nucleus and is known to vary greatly in bulk." Again,[203] he quotes Heidenhain's statement based on results obtained by physiological chemists and by himself: "Basichromatin and oxychromatin are by no means to be regarded as permanent unchangeable bodies, but may change their color reactions by combining with or giving off phosphorus."

The intracellular process is clearly discernible in the light of these observations: A constant reaction between adrenoxidase and nucleo-proteid granules is going on, the oxygen of the former and the phosphorus of the latter combining incessantly to liberate that heat energy which, as will be shown, is a necessary feature of the life of the cell, or rather, the life of its *proteid*.

How does this apply to the nerve-cell?

We have seen[204] that—from my standpoint—the neuron is not a mere cell, but an organ composed itself of nerve-cells, and that these nerve-cells, as far as the nerve proper is concerned, are the internodal segments—the portions of the nerve

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[202] Wilson: *Loc. cit.*, p. 222.
[203] Wilson: *Loc. cit.*, p. 224.
[204] *Cf.* this vol., p. 915 *et seq.*

extending between the nodes of Ranvier. Each of these segments is supplied, like all other cells, with its nucleus, located in the *myelin*, which corresponds, therefore, with the cytoplasm of ordinary cells. This suggests that the myelin must be the seat of the metabolic processes previously referred to. I have not only pointed out that the myelin is not a mere insulating substance, as now taught, but we have seen also that it is capable alone, and before the axis-cylinder is developed in regenerative processes, of transmitting nerve-impulses. Moreover, as stated by Sherrington,[205] "the date at which a nerve fiber completes its development, by acquiring a myelin sheath, indicates the time at which it becomes functionally active." As I interpret this fact, pointed out by Flechsig, it emphasizes the cardinal rôle the myelin plays in the production of the nerve impulse.

A question imposes itself in this connection: How, under these conditions, can "non-medullated" nerves, the fibers of Remak, generate or transmit impulses? Various authorities have held that these diminutive fibers are supplied with myelin as well as the "medullated" nerves. Boveri's[206] researches led him to conclude that they differed in no way from the latter, the axis-cylinder of the fibers of Remak being surrounded by a nucleated myelin sheath. Tuckett,[207] in a comprehensive study of the literature of the subject and after personal investigations, also concludes that "fibers of Remak consist of a nucleated sheath enclosing a core," and refers to the opinion of Ranvier,[208] Axel Key and Retzius,[209] Schiefferdecker[210] and Kölliker[211] that this core or axis-cylinder is composed of bundles of fine fibrils—a view now generally accepted. Moreover, it stains with methylene-blue and acid fuchsin, showing the presence of oxychromatin, *i.e.*, adrenoxidase, and is repeatedly referred to by Tuckett as "granular," though he ascribes this to the action of the stains. It is apparent, therefore, that all nerves have a similar structure, and that the gray color of the so-called "non-medullated" fibers is due merely to the fact that their myelin coat is thinner than that of larger nerves.

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[205] Sherrington: Schäfer's "T. B. of Physiol.," vol. ii, p. 792, 1900.

[206] Boveri: Abhand. d. k. bayerisch Akad. d. Wissenschaften zu München, Bd. xv, S. 499, 1885.

[207] Tuckett: Jour. of Physiol., vol. xix, p. 267, 1895-1896.

[208] Ranvier: "Traité technique d'histologie," p. 746, 1875.

[209] Axel Key and Retzius: "Studien in d. Anat. d. Nervens u. d. Bindegew," Bd. ii, S. 159, 1876.

[210] Schiefferdecker: Archiv f. mik. Anat., Bd. xxx, S. 436, 1887.

[211] Kölliker: "Handb. der Gewebel. des Menschen," Bd. ii, S. 30, 1893.

We have seen that in keeping with all other organs, a neuron is supplied with adrenoxidase, that this substance penetrates into its cell-body through the neuro-fibrils which enter the dendrites, and that they form a very fine network, especially dense around the nucleus. Now, this network is also termed the "cytoreticulum," and, as it takes methylene-blue, it is doubtless the homologue of the network common to all cells. As such, therefore, it is the living portion of the cell in the sense that, being immersed in the cytoplasm or ground-substance, it finds therein and, as in other cells, combines with the nucleo-proteid granules—an important constituent of nervous matter, as we have seen.[212]

Nervous substance contains various bodies which, until recently, were thought to be specific to this substance, viz., the phosphorized fats, which include myelin, protagon, lecithin, etc. Waldemar Koch,[213] however, has found them in other forms of protoplasm, including yeast cells, thus showing that nervous tissue differs only from all other tissues, in that it contains a larger proportion of these bodies. Their rôle is practically unknown. Thus, Halliburton[214] writes: "We know little of these substances from the chemical standpoint, and still less from the physiological." He also says, however,[215] referring to the "long list of substances to consider," and especially to extractives: "We can surmise that they are mostly waste products, as they are elsewhere." This coincides with the conclusion that my views suggest. Indeed, the substances that are brought to nerve-cells by leucocytes are, as elsewhere, proteids, sugars and fats. The proteid (nucleo-proteid) wastes are undoubtedly present: thus, as stated by Halliburton, small quantities of xanthin, hypoxanthin, lactic acid, uric acid and urea have been identified. The *fats* are represented by lecithin, which, in turn, yields fatty acid and glycerine, phosphoric acid and cholin. The *sugars* also appear in the form of galactose, obtained from the cerebrins, etc.

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[212] *Cf.* this vol., p 314.
[213] Waldemar Koch: "Decen. Publications of Chicago Univ.," vol. x, 1902.
[214] Halliburton: "Biochemistry of Muscle and Nerve," p. 66, 1904.
[215] Halliburton: *Ibid.*, p. 61.

All this suggests that the nerve-cell is not so complex a structure as it is now thought to be. Waldemar Koch,[216] in a searching analysis of the question, was led to conclude that "cortical gray matter, free from white fibers, besides containing no cerebrins, also contains no neurokeratin, cholesterin and kephalin or myelin. Gray matter, therefore," adds the author, "has a very simple composition, consisting of a mass of proteids, lecithin and the sulphur compound." As lecithin is a waste product, the constituents are further reduced to the proteids and the sulphur compound.

Now, these bodies include the nucleo-proteid and adrenoxidase we have found in all cells. By "proteids" Koch means Halliburton's three proteids.[217] Two of these are globulins, *i.e.*, fibrinogen (*extra corpore*) compounds. Referring to the third, however, Halliburton states that it is "a nucleo-proteid" which "contains 0.5 per cent. of phosphorus" and "coagulated by heat at 56 to 60°," the identical nucleo-proteid, in other words, that we have found in all tissues. The identity of the sulphur compound suggests itself after the data submitted when the relationship of the adrenal secretion to bronzing was studied. I then showed[218] that sulphur was a constituent of this secretion and therefore of the adrenoxidase circulating in the tissues at large—including, of course, the nervous tissues. Gamgee, in fact, says, referring to hæmoglobin, that "sulphur belongs to the albuminous part of the molecule"—the adrenoxidase—and the presence of this element indicates that "hæmoglobin belongs to the proteid compounds." (Halliburton[219]). The presence of the sulphur compound to which Waldemar Koch refers affords additional proof, therefore, to the effect that adrenoxidase circulates in the nervous system as elsewhere.

We are thus brought to the conclusion that the only appreciable difference between the nerve-cell and all other cells is the presence in the former of a larger proportion of fat. The nucleus contains a network which reacts to stains as does that of cells in general. The cytoplasm shows the same correspondence. The Nissl granules, which break down into fine dust in chromatolysis, are the homologues of the microsomes we have found in all cells; Halliburton says, in fact, that "microchemical methods have shown that they consist of nucleo-proteid."

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[216] Waldemar Koch: Amer. Jour. of Physiol., vol. xi, p. [illegible], 1904.
[217] Halliburton: *Loc. cit.*, p. [illegible], 1904.
[218] *Cf.* this vol., p. [illegible]
[219] Halliburton: Schäfer's "T. B. of Physiol.," vol. i, p. 27, [illegible]

The manner in which plasmatic adrenoxidase is supplied to a neuron is characteristic in that (interpreted from my standpoint) it is brought to them by minute capillaries, the neuro-fibrils. The cell-body of the neuron is supplied by fibrils which enter by way of the dendrites; the cells of the nerve proper are also supplied by fibrils, those which form their axis-cylinder, the plasma flowing upward or centripetally, in the minute tubes. But how does the adrenoxidase penetrate into the neural cells proper, *i.e.*, the internodal segments?

In the first volume[220] I submitted evidence showing that what was supposed to be a "supporting framework" in the myelin of each of the internodal segments, was in reality a "thread" which, according to Rezzonico and Golgi, forms a spiral or funnel-like threadwork around the axis-cylinder, and which, according to Tizzoni, communicates with the slits of Lautermann, or hollow canals described by this investigator, von Stilling, McCarthy, Wynn and others. These slits or canals and their threadwork evidently contain adrenoxidase, for they are stained with hæmatoxylin (McCarthy), an "oxychromatin" dye, we have seen, but which does not stain myelin. This is evidently a counterpart of the cytoreticulum we found in all cells, for as stated by Böhm, Davidoff and Huber:[221] "On boiling in ether or alcohol the entire medullary sheath of a nerve-fiber does not dissolve, but a portion remains in the shape of a fine network."

The cells of the nerve proper, therefore, like the cell-body of the neuron, contain their adrenoxidase network, and the meshes of this network bathe in a medium rich in phosphorus and fat. Heat energy is thus continuously liberated to sustain the life of the cell.

The wastes are eliminated through the lymphatic system as they are by other tissue-cells. "Although the nervous system is not known to be supplied with lymphatic vessels having definite walls, the circulation of lymph within the bundles of nerves is insured," as stated by Berdal,[222] "by the disposition of the intrafascicular connective tissue, the meshes of which represent lymphatic cavities." Such being the case, the plasma, after traversing the networks in the myelin, must either pass out through the neurilemma or at the nodes of Ranvier into the interneural lymphatic spaces. Another lymph-space is present between the bundle and its external covering, Henle's sheath. The cell-body, as is well known, is also supplied with a pericellular lymph-space in which chromatic granules are sometimes found.

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[220] *Cf.* vol. i, p. 535.

[221] Böhm, Davidoff and Huber: "T. B. of Histology," second edition, p. 157, 1905.

How is the nerve-impulse generated and what is its nature?

In the first volume[223] I adduced evidence which had led me to conclude that in all organs all manifestations of activity were due to an influx of oxidizing substance (adrenoxidase) into their cellular elements. We have seen[224] how essential oxygen is to nervous activity and that nervous elements are the seat of active metabolism. The presence of adrenoxidase in the networks of the cell-body, internodal segments and nuclei of a neuron readily accounts for these phenomena and for the waste-products enumerated; it affords also a clear explanation of chromatolysis, etc. That an exacerbation of activity in a neuron is brought about by a process similar to that which prevails in all cells is self-evident.

The details of this process again emphasize the need of regarding the neuron, not as a cell, but as an organ. The metabolic activity, chromatolysis and other phenomena indicating work, are practically limited to the cell-body, and yet the avalanche phenomenon and other facts show that the nerve proper is itself a source of nervous energy. On the other hand, a group of neurons—or rather of their cell-bodies—is known to form "centers," capable not only of receiving impulses, but of co-ordinating them and of transmitting the transformed impulses through their neuraxons, the nerves. It becomes a question now whether the cell-body of a neuron is itself the source of the nerve-impulse or whether this function falls solely upon its neuraxon or nerve.

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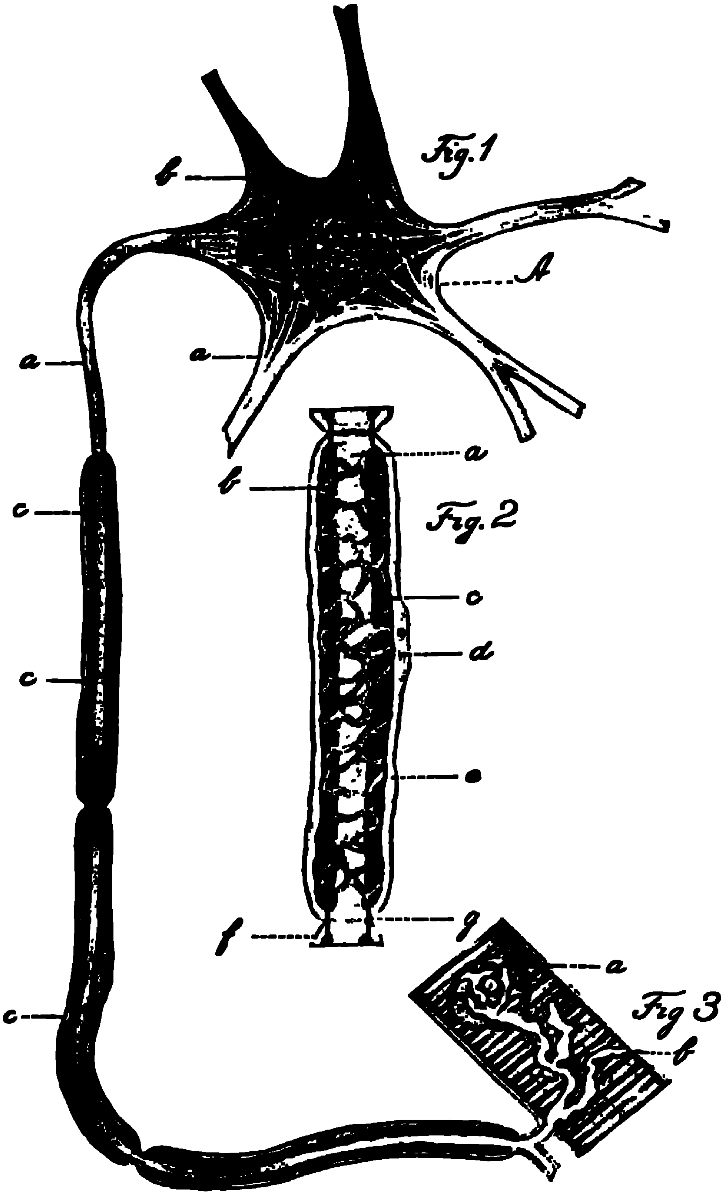
[222] Berdal: "Nouveaux éléments d'histologie normale," p. 153, 1894.
[223] *Cf.* vol. i, p. 120, in the first three editions.
[224] *Cf.* this vol., p. 915.

The prevailing view that the cell-body initiates nerve-impulses is based upon the fact that electric or mechanical stimulation of a center will awaken peripheral manifestations through the nerves it governs; but this only shows that the cell-bodies forming the center are endowed with a property more or less marked in all cells, *i.e.*, irritability. Again, a cell is not generally endowed with more than one function; and co-ordination, such as that shown by spinal "cells" in a beheaded frog, which will enable the animal to brush off a corrosive substance dropped on its back, is of such high order that it is only because it is a demonstrated fact that any cell or aggregate of cells other than those of the cortex can be regarded as possessing such powers. That in addition to this power, the cell-body is able to generate a nerve-impulse is not only improbable, but as shown below, its own irritability—the same irritability that causes a muscle to contract or a gland to secrete when stimulated—enables it to cause its neuraxon or nerve itself to generate and transmit impulses adjusted as to intensity, rhythm, duration, etc., to the needs of the peripheral organ. Briefly, the cell-body of a neuron is solely, from my view-point, a *co-ordinating center*, supplied with a chain of cells, the internodal segments constituting its neuraxon or nerve, and which cells are the source of all the impulses transmitted by the neuron.

The manner in which the cell-body causes its nerve to produce a stream of impulses is relatively simple. We have seen, by the upward flow of tetanotoxin, that the adrenoxidase-laden plasma circulates centripetally in the fibrils forming the axis-cylinder, and that a part of it at least (the rest passing laterally from the axis-cylinder into networks of the internodal segments) flows up the whole length of the nerve, up to the cell-body. At this point, the nerve forms a hillock, the implantation cone, which dips, so to say, in the cell-body's substance, and its fibrils (judging from the showings of Cajal's newer methods) likewise. Now, it is apparent that the *slightest contraction* of the cell-body or of the implantation cone around the bundle of axis-cylinder fibrils must, by compressing them, im-



THE NEURON AS AN ORGAN. [Sajous.]

Fig. 1. CELL-BODY OR CHIEF CELL. A, a, fibrils as capillaries for adrenoxidase-plasma; b, Nissl granules, as nucleo-proteid microsomes.

Fig. 2. TRUE NERVE-CELL. a, axis-cylinder fibrils as capillaries for adrenoxidase-plasma; b, network for distribution of plasma throughout myelin; c, myelin; d, cell-nucleus and nucleolus; e, neurilemma; f, tip of next cell; g, Ranvier's node. In cells on neuron: c, slits of Lautermann.

Fig. 3. MUSCULAR TISSUE. a, motor ending; b, terminals of fibrils of axis-cylinder, in which adrenoxidase-plasma (and tetanotoxin) flow upward or centripetally.

pede the flow of adrenoxidase-plasma throughout the whole length of the nerve, and by thus increasing the pressure of this substance in the axis-cylinder, cause an excess of it to flow into the networks of the internodal segments or true nerve-cells. A sudden influx of oxygen-laden adrenoxidase into the phosphorus-laden myelin from end to end of the nerve cannot but as suddenly incite a reaction entailing, as in all cells, the liberation of energy.

This conception meets the various biological and experimental facts that have stood the test of time. Nervous energy has been identified with electricity since Galvani's discoveries; and the galvanometer, the current generated by the electric organs of the sheath-fish, the torpedo, the electric eel and various vegetable and animal tissues have all served to show that this view is sound. Thus, the row of internodal segments around the axis-cylinder, or what I regard as the only true nerve-cells, correspond in their general structure and composition with the "electric cells"—also long and slender—in the spinal cord of the electric eel. Again, as stated by Verworn,[235] "these electric organs have the same embryonic origin as cross-striated muscles, to which also in their adult state, they possess great similarity." I have submitted evidence showing[236] that muscular contraction is also produced by a sudden influx of adrenoxidase (oxidizing substance)—MacMunn's myohæmatin—into the muscular elements where they also combine with a substance containing nucleo-proteid—myosinogen and a carbohydrate, glycogen. The same correspondence asserts itself in other directions: Sensory nerves are structurally similar to motor nerves, the sensitive "end-organs" affording *prima facie* evidence that irritablity is the initial factor when nerve impulses are to be incited. This same irritability accounts for the fact that electric stimulation in the course of a nerve will evoke impulses, since the nerve-cells themselves are stimulated. Heat increases and cold decreases the velocity of an impulse: this is readily accounted for by the fact that myelin is liquefied by heat and hardened by cold. Alcohol impairs conductivity: this is because it becomes oxidized at the expense of the adrenoxidase. Indeed, it is an established fact that deprivation of oxygen and asphyxia by anæsthetics likewise impair the conductivity of nerves.

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[235] Verworn: *Loc. cit.*, p. 260, 1899.
[236] *Cf.* vol. i, p. 261, in the first three editions.

The fact that my interpretation explains these various features of the question seems to me to indicate that, in its general lines at least, it is poised on a solid foundation. Although the nerve-impulse has been identified with electricity, the process through which it is produced and its nature as a physiological entity have not been found. Indeed, in the last edition of his work, Landois[227] states that "the nature of the physiological nerve-stimulus in the normal body is not known,"—a fact readily accounted for when we realize that the two original sources of energy, the granulations of leucocytes and adrenoxidase, were themselves unknown.

And this applies to all the living structures of the organism, since, in the light of my views, all cells of whatever kind are perpetuated as living entities through the intermediary of these two sources of energy. One salient feature asserts itself, however, in this connection, viz., the masterful rôle of adrenoxidase. The proteid is, in truth, the living substance, but it is as dead substance that it enters the body. It is through the presence of adrenoxidase that it is endowed with life in the leucocyte, and that its identity as living tissue is sustained in the cell. Its active principle, acting as catalytic, is the true vitalizing agent in this process, since it is able, as such, to raise the oxidizing activity of the oxygen it carries to a very high potency, and thus to provide the proteid with a correspondingly great amount of heat-energy, by combining continuously with the phosphorus of the nuclein to which the proteid is anchored. As the proteid contains all the chemical constituents that render it *viable*, the heat-energy thus supplied to it increases the vibratory amplitude of its atoms to that compatible with the living state, and it becomes *living* tissue. In other words, heat-energy becomes transformed into vital energy. Adrenoxidase, as catalytic and oxidizing agent, is thus the life-giving and life-preserving constituent of all cells.

The proteid lives as long as its physical properties are such as to enable it to subserve adequately its function in the cell;

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[227] Landois: "T. B. of Human Physiol.," Amer. edition, p. 631, 1905.

there comes a time, however, when worn, it must be removed. Here new factors are introduced, viz., the various hydrolytic triads, proteolytic, lipolytic and amylolytic (also brought to the cell by leucocytes, we have seen), to break down the proteids and what carbohydrates may be adjoined to them—fats in the nerve-cell, glycogen in the muscle-cell, etc. Again does adrenoxidase assume control: Itself a part of the triads, it carries on its rôle as "ferment of ferments" in each triad, and submits to hydrolytic cleavage the worn-out constituents of the cell, thus converting them into benign and eliminable waste-products.

The two phases of the living process, the building up of living tissue, *anabolism*, and the breaking down of worn-out tissue, *catabolism*, are thus incited and governed by the oxygen-laden secretion of the adrenals.

On the whole, the evidence submitted in this and other sections appears to me to warrant the following conclusions:

As to the conversion of proteid into living substance and its maintenance as such in the cell: (1) *the proteid constituent of the nucleo-proteid granules is the focus of the vital process, the true living substance;* (2) *although it enters the body lifeless, it contains all the constituents of living substance and acquires life in the leucocytes through the agency of the adrenoxidase these cells contain;* (3) *adrenoxidase being both a catalytic and an oxidizing agent it causes, when combining with the phosphorus-laden nuclein of the leucocyte's nucleus, the liberation of sufficient heat-energy to amplify the atomic vibrations of the proteid to a point compatible with life, and thus transforms it into living substance;* (4) *when the proteid enters the cell and is drawn to the network along with its nuclein moiety, its living state is also sustained by adrenoxidase, but by that constituting the network, while the nuclein with which this adrenoxidase combines is that linked to the proteid;* (5) *life is perpetuated in the cell by the incessant arrival of particles of living substance which continue their existence therein, linger for a time, then leave the cell as waste.*

As to the functional mechanism within the cell: (1) *The physico-chemical processes that sustain life occur in, or around, the networks of the nucleus and cytoplasm, the affinity of the* *adrenoxidase granules composing these networks for phosphorus causing them to attract the nucleo-proteid granules and to combine with them;* (2) *in the nucleus the two bodies are replaced, gradually as they are being used, by the absorption of granules of both kinds from the exterior;* (3) *the network of the cytoplasm is also rebuilt as its granules are being used, but by the nucleus, which projects fresh granules of adrenoxidase into its threads;* (4) *the nucleo-proteid granules are continuously being taken up by the network from the accumulations of these granules stored in the cytoplasm between its meshes;* (5) *the ground-substance between the meshes of the network is passive in the vital process, being a depository for the stored nucleo-proteid granules, waste products, salts, etc.;* (6) *when the nucleo-proteid granules, and what carbohydrates may be present, are worn out, they are broken down by the various hydrolytic triads (ferments) also brought to the cell by the leucocytes, and converted into benign wastes which are cast out through the vacuoles into the lymph spaces and ultimately eliminated.*

In the nervous system, the biochemical processes involved correspond, on the whole, with those of cells in general. Yet the neuron, as previously stated, is not a cell-unit as now generally taught, but an organ; it presents, moreover, structural peculiarities as to the manner in which its blood is distributed to its cells. As to this feature of the problem: (1) *nerve-cells differ from ordinary cells in that they are supplied with adrenoxidase by capillaries (fibrils) that empty directly into their networks;* (2) *in the chief cell of the neuron, the "cell body," these capillaries, or "neuro-fibrils," reach the network or cytoreticulum, which is, as in other cells, composed of adrenoxidase (oxychromatin) granules, and immersed in a plasmatic cytoplasm containing groups of nucleo-proteid (basichromatin) granules;* (3) *in the neuraxon or nerve, the axis-cylinder fibrils allow the adrenoxidase to traverse their walls (as it does through those of ordinary capillaries) and to enter the slits of Lantermann in the myelin, which slits in turn open into the networks in this substance.*

As to the functional relationship between the cell-body of the neuron and its neuraxon or nerve, the manner in which nerve impulses are produced, and the nature of these impulses: (1) *the "cell-body" of a neuron is not a nerve-cell but a co-ordinating* *center endowed with marked irritability; as such it can react to nervous impulses and cause its own neuraxon or nerve to generate such impulses;* (2) *it performs this function by contracting around the upper end of the axis-cylinder fibrils that project into it; the* (*centripetal*) *current of adrenoxidase-laden plasma being thus impeded* (*proportionally as to degree and time, with the vigor and duration of the impulse*), *the pressure of this fluid in the fibrils is increased throughout the whole length of the nerve, and an excess of adrenoxidase is driven into the networks of the myelin;* (3) *the phosphorus- and fat-laden myelin being the cytoplasm of the true nerve-cell* (*the internodal segments around the axis-cylinder*), *the network of adrenoxidase immersed in it is the focus of chemical activity as in other cells, and the source therefore of the nerve impulse;* (4) *the true nerve-cells are the biochemical homologues of the cells constituting the electric organs of various animals, and the nerve impulse corresponds* (*as to its nature*) *with the impulses derived from such organs;* (5) *the waste products, which include lecithin, cerebrin, purin bases and phosphoric acid, are eliminated from nerve-cells, as elsewhere, into lymph channels, viz., into the peri-cellular lymph spaces around the cell-bodies; into the spaces between the nerves in nerve-bundles, and into the space between these bundles and their outer covering, Henle's sheath.*

Adrenoxidase is thus shown to be the dominating principle in nerve-cells as well as in all other cells. It is able not only to endow non-living though viable proteids with vitality by bringing into play and governing the activity of various other physico-chemical bodies, but it can also sustain the vital process it has initiated, in all the cells of an organism. Again, while we may define Life, with Herbert Spencer, as "the continuous adjustment of internal relations to external relations," or with de Blainville as "the two-fold internal movement of composition and decomposition, at once general and continuous," the need of a governing and vitalizing physical principle has asserted itself by the introduction into the problem at various times of an exogenous "vital principle," or a separate and distinct "vital force," etc. But such agencies do not bear close scrutiny. Spencer[228] closes his chapter on the "Dynamic

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[228] Spencer: "Principles of Biology." vol. 1, p. 122, 1898.

Element of Life" with the statement: "We find it impossible to think of Life as imported into the unit of protoplasm from without; and yet we find it impossible to conceive it as emerging from the co-operation of the components." The active principle of adrenoxidase was unknown at the time these lines were written; its rôle, we have now seen, is precisely to endow the protoplasm with life without introducing a problematic factor into the process.

General Remarks.—Notwithstanding the considerable and painstaking labor that physiologists have bestowed upon the questions of absorption, assimilation and metabolism—which labors have furnished much of the evidence I have submitted in these pages—none have remained shrouded in greater obscurity. As to absorption of food products from the intestine, Howell, for instance, says:[229] "The energy that controls absorption is furnished........by the wall of the intestine, presumably in the epithelial cells. It constitutes a special form of imbibition which is not yet understood." According to prevailing views, the products of gastro-intestinal digestion should be found in the blood after their passage through the walls of the intestine: Mendel writes:[230] "Beyond the intestinal wall, in the blood and lymph stream, the cleavage products seem, for the most part, to be missing." The fluid proteids should also penetrate freely to the tissue-cells: Howell states: "The proteids of the blood, which are supposed to be so important for the nutrition of the tissues, are practically indiffusible, so far as we know. It is difficult to explain their passage from the blood through the capillary walls into the lymph." The prevailing knowledge of the intracellular exchanges is even less satisfactory: Sir Michael Foster[231] closes a study of metabolism in his text-book with the statement that, after all, it "consists mostly of guesses and gaps."

The reason for this deplorable lack of knowledge upon questions which represent the very foundation of all that we, physicians, should thoroughly understand before pretending at all to study diseased states intelligently, is not difficult to find.

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[229] Howell: "T. B. of Physiology," p. 772, 1910.
[230] Mendel: Med. News, May 20, 1905.
[231] Foster: cited by W. G. Little, Liverpool Med.-Chir. Jour., Jan., 1905.

Without the functions the data submitted have led me to attribute to the adrenal secretion and the granulations of leucocytes, the problems of respiration, absorption, and metabolism are absolutely unfathomable.

CHAPTER XVI.

THE PITUITARY BODY AS GOVERNING CENTER OF VITAL FUNCTIONS.

THE PITUITARY BODY AS THE GOVERNING CENTER OF THE BODY'S IMMUNIZING FUNCTIONS.

The prevailing view is that the pituitary body is a secreting gland. In truth, this conception has never been carefully analyzed by its sponsers—a deplorable fact. No greater fallacy could be vouched for than the belief that because an extract of a given organ gives rise to physiological effects, that organ is a ductless gland. Indeed, on that plea the pituitary should now be granted *four* internal secretions, while the most active extract is derived from the neural or posterior lobe, which, as emphasized by Biedl, Swale Vincent, myself and others long ago, is not a glandular organ at all. All these extracts act pharmacologically but *not* as internal secretions.[1]

In the first volume I contended that the anterior lobe of this organ contained sensory cells which had for their purpose to detect the presence of toxic substances in the blood. Considerable evidence was also submitted to show that these sensory structures could, in case of need, and through the intermediary of the adrenals and thyroid particularly, enhance the functional activity of the defensive functions. We have likewise seen that these organs are dominated by the sympathetic system, and that I regard the posterior or neural lobe of the pituitary as main nucleus or center (previously unlocated) of that system.

That such a protective function actually exists in man is further sustained by the fact that its presence is clearly discernible throughout the entire phylogenetic scale, at least down to and including mollusks. "Near the base of the stem of each ctenidium" [gill-combs], says Ray Lankester,[2] "is a patch of the epithelium of the body-wall, peculiarly modified and supplied with a special nerve and ganglion. This is Spengel's olfactory organ. which *tests* the *respiratory fluid,* and is persistent in its position and nerve-supply throughout the group Mollusca." To this group of cells Lankester gave the name "*osphradium.*" Parker and Haswell[3] more specifically define the functions of this organ, viz., "to test the *purity* of the water entering by the respiratory current."

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[1] See also pages 173 and 511 in the first volume.

[2] Ray Lankester: Art. "Mollusca," "Encyclo. Britannica," ninth edition, vol. xvi, p. 636.

Ascending from the Invertebrates to the Vertebrates, we find this same organ in the lowest of fishes, the lancelet or amphioxus. In this lowly animal, the water, which enters the mouth and traverses the entire body, also subserves the respiratory function (Lankester).[4] "The mouth of Amphioxus would seem to be well guarded against the intrusion of noxious substances," writes Willey,[5] "everything entering the mouth has to pass through a vestibule richly provided with sensitive epithelial cells." The relations of these cells are shown in Fig. 1. Lloyd Andriezen[6] likewise refers to sensory structures in amphioxus constituting "a nervous organ," which is "sensitive to the *quality* of the water which passes over it," and remarks that "this is no isolated phenomenon, for we find a striking analogy in the osphradial organ and ganglion of Mollusca, which is situated at the entry of the mantle or respiratory chamber, and serves to *test* the quality of the water which passes over the respiratory organ." We thus have clear evi-

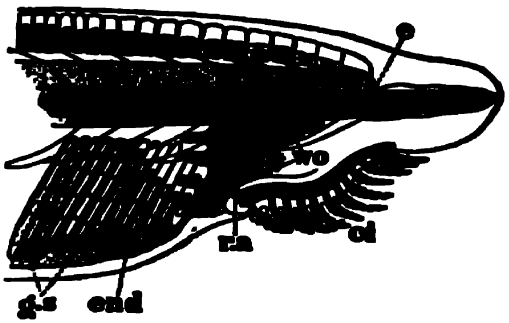

FIG. 1.—TEST-ORGAN IN AMPHIOXUS IN A YOUNG TRANSPARENT INDIVIDUAL. (*After J. Müller, slightly modified by Willey*).

wo, Ciliated epithelial tracts. *gs*, Gill-slits. *end*, Endostyle (the future thyroid). *va*, Down-growth of Aorta. *nt*, Spinal cord. *ch*, Notochord. *e*, Eye-spot. *ci*, Cirri.

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[3] Parker and Haswell: "Manual of Zoölogy," p. 277, 1900.

[4] Lankester: *Loc. cit.*, vol. xiv, p. 258.

[5] Willey: "Amphioxus and the Ancestry of the Vertebrates," p. 19, 1894.

[6] Lloyd Andriezen: Brit. Med. Jour., Jan. 13, 1894.

dence to the effect that these lower forms, at least, are endowed with a specific apparatus, which, though primitive, has for its purpose to protect the *oxygen-bearing stream*, and, through the latter, the body at large.

A feature of great importance in this connection, however, is the evident presence of two structures fulfilling correlated functions. While Lankester refers to "a patch of epithelium" . . . . "*supplied* with a special *nerve* and *ganglion*," located at the base of the gill-combs in Mollusks, he includes all these structures in Spengel's "olfactory" test-organ. The importance of this lies in the fact that we have in this dual organ a counterpart of the pituitary body, which is composed, as is well known, of two lobes, one epithelial and the other neural. As far back as 1881 Julin[7] showed that in Ascidians, or sea-squirts, which belong to a subclass below amphioxus (the Urochorda), the *sub*neural gland, which underlies a ganglion embedded in the mantle of these animals (and which ganglion represents the general center of their nervous system), was similar in structure and relations to, and a counterpart of, the pituitary body of the Vertebrates. Lloyd Andriezen[8] not only confirmed this fact more recently, but as the result of comprehensive histological study of the subject in ammocœtes (larval petromyzon) and lower forms, affirmed the previously supposed two-fold function of this organ. "Even in the highest mammals and *man*," says this investigator, "it has a two-fold structure and represents a double organ."

The close relationship between the two organs is clearly shown in Fig. 2, a longitudinal section of the upper portion of a young clavelina, or sea-squirt, shortly after metamorphosis. Although drawn by van Beneden and Julin, the illustration is a part of one reproduced from Willey's treatise, and the lettering in the latter is intentionally preserved. The water enters *m*, the mouth, is tested by *hy*, the hypophysis, *i.e.*, the pituitary body, and the latter, as clearly shown, is in immediate contact with *g*, the ganglion.

This affords additional testimony in another direction. In the first volume I stated that the pituitary body was not only connected with the adrenals, but also that the fibers from the former organ ultimately reached the latter by a direct nerve path, even though the adrenals were located in so remote a position as above the kidneys, *i.e.*, amongst the abdominal viscera. In Fig. 2, *vn*, the visceral nerve (which, with the ganglion, represents the animal's entire central nervous system), as may be seen, extends from *g*, the ganglion, to *int*, the intestines. Benedin and Julin allude to this nerve as the *cordon ganglionnaire viscéral*, or "visceral ganglionic cord," which starts "from the posterior end of the adult cerebral *ganglion*, and, proceeding along the dorsal side of the pharynx above the dorsal lamina, becomes lost among the viscera" (Willey[9]). Huxley and Martin,[10] moreover, refer to the "patch of sensiferous epithelium in the roof of the inhalant siphon" or test-organ (Lankester's osphradium) as being "immediately connected" with "the parieto-splanchnic ganglion." We have seen that the abdominal main path to the adrenals is the great splanchnic nerve. It is evident, therefore, that even in so low a group as Mollusca, which includes the bivalves, shell-fish, clams, oysters, mussels, etc., the univalves, snails, periwinkles, etc., and the cuttle-fishes, squids, octopi, etc., though supplied with very limited nervous systems, the fundamental nerve structure or cephalic ganglion is intimately connected with the hypophysis or pituitary body—an early prototype of the system I have traced in man.

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[7] Julin: "Recherches sur l'organis. des ascidies simples," Archives de biol., vol. ii, pp. 59, 211, 1881.

[8] Lloyd Andriezen: *Loc. cit.*

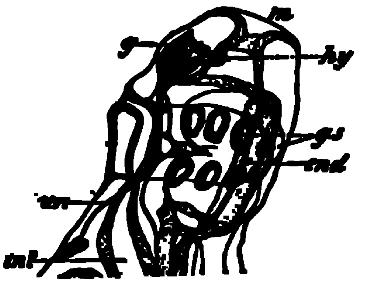

FIG. 2.—OSPHRADIUM OR TEST-ORGAN OF A YOUNG ASCIDIAN.

m, Mouth. *hy*, Hypophysis (Pituitary), the test-organ. *g*, Ganglion. *end*, Endostyle (future thyroid). *gs*, Future gill-slits. *vn*, Visceral nerve. *int*, Intestine. (*Drawn after van Beneden and Julin.*)

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[9] Willey: *Loc. cit.*, p. 224.
[10] Huxley and Martin: "Practical Biology," p. 312, 1892.

A confusing feature of the whole problem has served greatly, however, it seems to me, to obscure our knowledge of the functions of the pituitary body. We have seen that the osphradium, the patch of epithelial cells forming Spengel's organ, and to which water-testing functions have been ascribed, is referred to by various zoölogists as an *olfactory* organ. Again, the pituitary body, as we know, is connected with, and forms part of, the infundibulum in craniate Vertebrates. The uniformity of this anatomical relationship obviously suggests a functional connection between them, especially since, in the course of its embryological development, the pituitary becomes, in most forms, detached from the mouth to actually fuse with the infundibulum—evidently a purposeful step. Von Kuppfer[11] having found the homologue of the olfactory organ of Amphioxus in a region quite remote from the infundibulum in craniate Vertebrates, concluded that there could be no relation between them, and that the olfactory organ of Amphioxus was the homologue of the median rudimentary lobe of the embryo which ultimately becomes the true olfactory lobe, *i.e.*, that connected with the sense of smell.

Von Kuppfer's view, which has been accepted by a number of investigators, though apparently poised on a sound foundation, is invalidated by the fact that he *assumes* that there exists but one structure supplied with specific olfactory cells, whereas the nature of the functions of the osphradium in mollusks, and the corresponding test-organ in Ascidians, Amphioxus, etc., and other facts, clearly suggests that there may be *two*. This important question can only be settled by showing that in the higher mammals there exists, besides the olfactory lobe of the organ of smell, another region supplied with olfactory cells and intimately connected with the pituitary body. That such is actually the case is shown by the following facts:—

Nearly forty years ago, Peremeschko[12] described a transverse slit, or cavity, between the glandular elements of the anterior lobe of the pituitary and the partition which separates it from the posterior lobe. This cavity was found by him to be lined throughout in man with *ciliated epithelium*. Wilhelm Müller[13] also found that the internal wall of this slit, forming part of the interlobular partition, was lined with this epithelium. Cadiat[14] and others have since confirmed these observations—all made, however, before the more advanced histological methods had been developed. This region of the pituitary body was likewise studied by Gentès,[15] by the Golgi method, in the higher mammals, namely, the cat and dog. He found that the anterior lobe was, in reality, composed of two parts, the glandular and neural, the latter forming the *inner* wall of the partition between the two lobes. The epithelium revealed by ordinary stains was shown, by the Golgi method, to contain interstices penetrated throughout by sensory cells, each cell sending broad processes to the free surface and into the depths of the epithelial layer. The latter's structure, he states, recalled exactly that of the *olfactory area of the nasal mucous membrane.*

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[11] Von Kuppfer: Archiv f. mikr. Anat., Bd. xxxv, S. 469, 1890.
[12] Peremeschko: Virchow's Archiv f. Anat. u. Phys., Bd. xxxviii, S. 329, 1867.

The value of these observations is enhanced by the fact that Gentès does not refer to the researches of zoölogists, whose labors, of course, were beyond his normal field. We thus have, in his work, an independent confirmation of the existence in the pituitary body of the higher mammals, of a structure totally independent of the organ of smell, and which, even in the lowly mollusk, has been accorded the rank of a *protective* organ—precisely that recognized by Spengel in Ascidians, *i.e.*, to "test the respiratory *fluid.*"

One of the functions I have ascribed to the pituitary body of man is none other than this, namely: to detect any toxic substance that may be present in the blood, the organism's oxygen carrier and, therefore, its respiratory *fluid*, after the water-vascular system has become a blood-vascular system.

As we will see farther on, this harmonizes with the phylogeny and embryology of both lobes of the pituitary body.

Drugs, toxins, venoms, toxic physiological wastes, etc., assume, under these conditions, the position of foreign elements in the blood-stream. On the other hand, the presence in the human pituitary body of nerve-cells recalling those of an organ capable of reacting to innumerable kinds of odoriferous emanations and therefore to the immeasurably small particles of which they are composed, explains why the body responds actively to the influence of so many of these toxics and why so minute a dose of a given remedy, $^1/_{600}$ grain (0.0001 gramme) of aconitine, for example, or an equally diminutive quantity of vaccine virus can evoke, in the human organism, such marked phenomena as those observed.

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[13] Wilhelm Müller: Jenaische Zeit. f. Naturw., Bd. vii, S. 327, 1873.

[14] Cadiat: "Anatomie Générale," cited by Guépin, Tribune médicale, Dec. 10, 1891.

[15] Gentès: C. r. de la Soc. de biol., T. lv, p. 160, 1903.

It is evident, therefore, that we are dealing, in this connection, with the *foundation of the organism's auto-protective mechanism*—one indeed, as I have stated in the first volume (and as will be further emphasized in the present one), whose beneficial influence we can, through our remedies, govern at will. But I also pointed out therein that it was through the intermediary of the oxidizing substance—adrenoxidase—that this influence was exercised. How is the distribution of this all-important substance governed, *i.e.*, hastened or retarded? If, as I hold, the pituitary body is a structure through which disease may be controlled, what constitutes within its precincts the keyboard—using Jacques Loeb's comparison—which we, as artists, must utilize to attain this object?

The purpose of this chapter is to answer this question.

THE PITUITARY BODY AS A NERVE-CENTER.

In the first volume, I ascribed to the pituitary body the function of a general nerve-center. While urging that it was the anterior lobe of this organ which carried on the function referred to in the preceding section—that of "test-organ"—owing to its identity as the governing center of the adrenals, I held that the posterior or "neural" lobe, which is linked with the anterior, and connected by its pedicle with the base of the brain, was the primary source of certain motor impulses now thought to originate in the bulb or medulla oblongata. The anatomical relations of the two organs to which I attribute such commanding importance is well shown in the illustration on page 963, in the ascidian. The ganglion adjoined to the pituitary body *hy.* is not merely the cell-body of a neuron, as the term implies; as stated by Jacques Loeb:[16] "In ascidians the central nervous system *consists* of a central ganglion." It is, in other words, the source of *all* motor impulses transmitted to the various organs of these animals.

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[16] Jacques Loeb: "Comparat. Physiol. of the Brain," p. 35, 1902.

In the higher Chordata, which include all vertebrates—fishes, amphibians, reptiles, birds and mammals and, therefore, man—the anatomical relations remain the same as in the Ascidians. Thus, as stated by Parker and Haswell[17] in reference to the development of the pituitary is this phylum: "The floor of the diencephalon grows downward into a funnel-like prolongation, the *infundibulum:* with this the pituitary diverticulum of the pharynx comes into relation, and there is formed partly from the dilated end of the diverticulum, partly from the extremity of the infundibulum, a gland-like structure, the pituitary body or hypophysis, always situated *immediately in front of the anterior extremity of the notochord.*" In other words, from the lowly Ascidian, which represents one of the simplest organisms classed among the Chordata, up to man, the pituitary body is connected with, and forms part of, the upper extension of spinal cord in the base of the brain. Its infundibular extension, as is well known, is the *neural* or posterior lobe of the pituitary, which is separated from the anterior or "glandular" lobe by the partition in which the "test-organ" is embedded.

That the pituitary body fulfills important functions in the higher animals as well as in the lower forms is strikingly suggested by the results that follow removal of the organ, especially when it is fully developed, as in adult animals.

Marinesco[18] trephined the bone underlying the organ and destroyed the latter by cauterization in cats. Two died almost immediately; two twenty-four hours later, one lived four days, another five days, and the last eighteen days. No cause for death could be found other than the destruction of the pituitary. Dastre[19] performed similar experiments. All the animals died. Alluding to Marinesco's experiments and to others by Vassale and Sacchi,[20] Schäfer states that the symptoms observed were: "(1) diminution of the body temperature; (2) anorexia and lassitude; (3) muscular twitchings and tremors developing later into spasms; (4) dyspnœa." In their original article, Vassale and Sacchi mention an instance in which the pituitary was only partially destroyed; although the characteristic phenomena followed and lasted about three weeks, the animal recovered and remained healthy eleven months. The incomplete destruction of the organ was then confirmed. They state that animals die promptly after a complete operation. Andriezen[21] says that destruction of the pituitary causes apathy and psychical depression, marked relaxation of the muscular system, and muscular spasm. Co-ordination and equilibrium are greatly impaired. The temperature becomes abnormally low; nutrition is reduced; cachexia supervenes and death follows. Caselli[22] after removal of the gland in young animals observed cachexia, glycosuria, and death. Pirrone[23] ascertained experimentally, among other facts, that "the results of the suppression of its functions are disturbances of mobility, great depression, rapid emaciation, cachexia and death." He was also led to conclude that "although the exact functional mechanism of this gland is not as yet well understood, it is evident that it is of the greatest importance to the economy," and furthermore, that "although a partial lesion is compatible with existence, its total removal irrevocably leads to death." Krönlein and Von Eiselsberg[24] destroyed the pituitary body in cats. The procedure invariably proved fatal. Friedmann[25] removed the organ from several kittens from 3 days to 10 weeks old. All died except one, which showed "an insignificant staggering" and lived two and one-half months. With Maas[26] the same observer also removed the pituitary in eighteen animals. Twelve died in from one to thirteen days; two died of complications; three which continued to live, were found still to possess a part of their organs; the remaining one, notwithstanding complete removal, lived three and one-half months; after which it was killed. Death might be ascribed, in these younger animals at least, to the severity of the operative procedure adopted, since, as I have stated in the first volume, the thymus fulfills to a certain extent the functions of the adrenal system until the organs composing the latter are developed. Very young mammals correspond with the lower vertebrates (toads, frogs, etc., for instance) in this particular, the morbid effects of removal growing in intensity as the higher mammals are reached.

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[17] Parker and Haswell: "T. B. of Zoölogy," vol. ii, p. 96, 1897.
[18] Marinesco: Bull. de la Soc. de biol., June 4, p. 509, 1892.
[19] Dastre: Richet's "Dict. de physiol.," vol. i, p. 169, 1895.
[20] Vassale and Sacchi: Arch. ital. de biol., vol. xxii, p. 123, 1895.

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[21] Andriezen: Brit. Med. Jour., Jan. 13, 1894.

[22] Caselli: "Studii anat. e sperim. sulla fisio-pat. della glandula pituitaria," 1900.

[23] Pirrone: La riforma medica, Feb. 25, p. 205, 1903.

[24] Krönlein and Von Eiselsberg: Trans. German Surgical Assoc., Apr. 6, pp. 110, 111, 1904.

[25] Friedmann: Berliner klin. Woch., May 12, p. 436, 1902.

[26] Friedmann and Maas: *Ibid.*, Dec. 24, p. 1213, 1900.

The most decisive experiments, however, were performed by Massay,[27] whose object was to ascertain whether all the animals did not die owing to the severity of operation. After removing a disc of bone 6 millimeters in diameter from beneath the pituitary body of two dogs, he rapidly destroyed the organ with thermocautery. The next day both animals were profoundly asthenic and unable to stand, while spasmodic twitchings and "convulsive trembling" occurred. On the third day, these phenomena became more marked; coma supervened, and the animals died. The pituitary body was found cauterized in both animals and congestion of the nerve-centers was noted. In a third dog, the same procedure was resorted to, but in two stages. The pituitary body was exposed as in the two other instances, and the animal *allowed to recover*. Two secondary hæmorrhages and marked hyperthermia occurred, but a week later all signs of discomfort had disappeared. The pituitary was then destroyed with galvano-cautery. On the following day, the symptoms observed in the two other dogs appeared, viz., marked asthenia, with occasional paroxysms of muscular spasm or very violent convulsions, *hypothermia*, and "very rapid" heart beat. They became gradually more intense, and the lethal course observed in the other animals followed.

It is when the fatal influence of removal of the pituitary body is compared with the effects of removal of the *brain* that the functional importance of the former organ asserts itself.

Beginning with the lower vertebrates we have Wilber's frog,[28] which lived five years after removal of its cerebral hemispheres. "During all this period the animal never once showed signs of any initiative, its only movements being very slight and attributed to muscular ennui, like that of persons asleep. The eyes, optic nerves, and optic lobes of the brain were uninjured, and the animal could evidently see, but without understanding. The most attractive frog food put before it was absolutely unnoticed, and it has been fed every day for five years by an attendant, who would open its mouth, and with force push a bit of fresh meat or fish far enough back into its throat to arouse the reflex mechanism of swallowing. If touched, it would move or leap; if placed in water, it would swim until *some support was reached; if turned upon its back, it would promptly and vigorously right itself.*"

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[27] Massay: Ann. de la Soc. roy. de sci. méd. et nat. de Bruxelles, T. xii, Fasc. 3, p. 1, 1903.

[28] Wilbur: Amer. Med., Jan. 7, p. 6, 1905.

In a higher vertebrate, the pigeon, the results are the same. "The results of ablation of the cerebral hemispheres in pigeons," says Schäfer,[29] "have been described in great detail by Rolando, Flourens, Longet, Vulpian and others. A pigeon so mutilated continues able to maintain its equilibrium and to regain it when disturbed. When placed on its back, it succeeds in regaining its feet. When pushed or pinched, it marches forward. Should it happen to step over the edge of the table, it will flap its wings until it regains a firm basis of support. When thrown in the air, it flies with all due precision and co-ordination. Left to itself, it seems as if plunged in profound sleep. From this state of repose it is easily awakened by a gentle push or pinch, and looks up and opens its eyes. Occasionally, apparently without any external stimulation, it may look up, yawn, shake itself, dress its feathers with its beak, move a few steps, and then settle down quietly, standing sometimes on one foot and sometimes on both. Should a fly happen to settle on its head, it will shake it off. If ammonia be held near its nostrils, it will start back. Should the finger be brusquely approximated to its eyes, it will wink and retreat. A light flashed before its eyes will cause the pupil to contract; and if a circular motion be made with the flame, the animal may turn its head and eyes accordingly. It will start suddenly and open its eyes widely if a pistol be discharged close to its head."

In the higher mammals, the absence of the influence of the brain on the life processes is none the less evident. Goltz's world-renowned dog which lived eighteen months after its brain (including part of the optic thalami and corpora striata) had been removed piecemeal, affords a striking example of this fact.

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[29] Schäfer: *Loc. cit.*, vol. ii, p. 709.

It walked about, curled itself up when about to sleep, reacted promptly to tactile impressions, thus showing that the sensory mechanism was not destroyed; it snarled and barked, withdrew its feet when these were placed in cold water, recovered its equilibrium when its feet were placed on the falling flap of a table; limped when one of its legs was accidentally hurt; rejected and showed dislike for meat rendered bitter with quinine, and refused more food when satiated.

Thus, in animals that live long enough after complete destruction of the pituitary body, morbid phenomena occur which point clearly to disturbance of cardinal vegetative functions, as shown by dyspnœa, hypothermia, rapid emaciation, asthenia, staggering, impairment of co-ordination and equilibrium, cachexia, spasms, convulsions and death. Removal of the hemispheres, on the other hand, disturbs in no way these functions—sensory or motor—thus showing that even in the higher mammals, all purely automatic functions, oxygenation, circulation, digestion, nutrition, locomotion, general sensibility, etc., are absolutely independent of the cerebrum. Indeed, Soury,[30] referring to the *cortex*, remarks: "The experiments of Steiner, Goltz, and Schrader show that the existence of this organ is not necessary in the performance of psychical functions considered in general as *inferior*." . . . . "It is the organ for superior psychical functions termed memory, association of ideas, acquired experience and reflection."

That the pituitary body is the seat of functions now generally attributed to the cerebral cortex is evident.

While experiments in animals, clinical and post-mortem observations have shown the existence in the cortex of areas which have been called "motor" because motor effects were elicited on stimulating them, this term is used merely for want of a better one and is not regarded by physiologists as necessarily meaning that the impulses transmitted from the cortex are necessarily "motor" in the sense usually given this word. "The terms 'motor area' and 'motor center,'" says Schäfer,[31] "are here used to imply those portions of the cerebral cortex which are directly connected by efferent projection fibers with the lower level centers (spinal cord, bulb and midbrain) from which impulses *producing* voluntary muscular action emanate." Again, "the application of the terms 'motor' and 'sensory' must be used rather *for purposes of convenience* than with a view to a rigid definition of function."

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[30] Soury: "Système nerveux central," T. I, p. 625, 1899.
[31] Schäfer: *Loc. cit.*, vol. II, p. 722.

Foster[32] says, however, in this connection: "The simplicity of the electrical phenomena resulting from cortical stimulation which we described, might at first sight lead us to conclude that the whole matter was fairly simple; and indeed, some writers appear to entertain the conception that in a voluntary movement such as that of the fore-limb, all that takes place is that the 'will' stimulates certain cells in the cortical area, causing the discharge of *motor* impulses along the pyramidal fibers connected with those cells, and that these impulses travel straight down the pyramidal tract to the motor fibers of the appropriate nerves, undergoing possibly some change at the place in the cord where the pyramidal fiber makes junction with the fiber of the anterior root, but deriving their chief if not their whole co-ordination from the cortex itself, that is to say, being co-ordinated at the very starting-point." He characterizes this view as "untenable," and the simplicity of the electrical phenomena as "misleading."

This obviously suggests that voluntary impulses are not themselves motor impulses, but stimuli which awaken such impulses in the spinal system. Indeed, referring to the experimental removal of both hemispheres in pigeons, Foster remarks:[33] "In this warm-blooded animal, as in the more lowly cold-blooded frog, the parts of the brain *below and behind the cerebral hemispheres* constitute a nervous machinery by which all the ordinary bodily movements may be carried out. The bird, like the frog, suffers no paralysis when its cerebral hemispheres are removed." The pituitary body evidently forms part of this region: "Until recently," writes Willey,[34] "it was generally thought that the infundibulum [the pedicle of the pituitary body] represented the anterior end of the brain, which had become bent downward and backward. Kuppfer has brought forward weighty reasons for doubting this. According to him, the infundibulum is essentially a down-growth or evagination from the *floor* of the brain, occurring *behind* the anterior terminal extremity of the brain."

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[32] Foster: *Loc. cit.*, p. 680.
[33] Foster: *Loc. cit.*, p. 641.
[34] Willey: "Amphioxus and the Ancestry of the Vertebrates," p. 282, 1894.

The functional relationship between the brain proper and this region below it is clearly defined in Foster's statement[35] that "on these the [cortical] motor area must have its *hold as on the spinal mechanisms.*" M. Duval[36] also identifies the character of the antero-lateral tracts themselves as extensions of the brain *per se* when he says: "When the antero-lateral columns are alone severed, *voluntary* action is abolished in the portion of the cord below the section. Evidently," he adds, "the antero-lateral columns serve at least in great part to transmit the *orders of the will;* they establish a communication between the cerebral centers and the *gray substances of the spinal cord.*"

The limits of this gray substance are apparently restricted to the spinal cord, judging from Duval's conclusion; but he gives the organ its true functional field when he also says:[37] "While the anatomist locates the upper limit of the spinal cord on a level with the occipito-atloidean articulation, for the physiologist it extends into the interior of the cranium . . . . about up to the sella turcica"—the bony pedestal, we know, of the pituitary body.

These facts plainly suggest (1) *that the pituitary body fulfills in the higher mammals as important functions as a nerve-center as the central ganglion does in the lower Chordata;* (2) *that it influences very markedly all the cardinal functions: respiration, oxygenation, nutrition, metabolism and locomotion; and* (3) *that it is the source of automatic motor impulses now believed to arise from the cerebral cortex.*

NERVE-PATHS FROM THE PITUITARY TO THE SPINAL CORD.

The evidence submitted in the foregoing section indicates that the pituitary body must be connected with the spinal cord by nerve-paths. As the spinal cord was shown to extend up to, and include, the infundibulum, which in turn terminates as the neural lobe of the pituitary, it becomes only a question whether the portion of the cord which extends above the bulb or medulla

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[35] Foster: *Loc. cit.*, p. 688.
[36] Duval: "Cours de physiologie," seventh edition, Paris, 1892.
[37] Duval: *Ibid.*, pp. 40 and 78.

oblongata contains such paths. Not only has their presence in this location been ascertained by various *investigators,* but it has been shown that the basal structures to which they are distributed are connected directly with the pituitary body by nerves, both of its lobes receiving an abundant supply.

As far back as 1903, Andriezen[38] referred to the posterior or neural lobe as "little beyond a neuroglia remnant." I have since pointed out[39] however, that neuroglia is not a mere reticulated framework of connective tissue, as now believed, and have adduced evidence showing that it differs from the latter both in its origin and chemical properties; that it originates from blood-vessels and penetrates into nerve-cells. Andriezen himself[40] described neuroglia-cells connected with blood-vessels, *i.e.,* "ensheathing the vessels of the brain"—the purpose of these cells being, in his opinion, to prevent undue expansion of the cerebral vessels. The view of Golgi, Clouston and others that neuroglia supplies nutrition to the nerve-cells; the many allusions to the "chromatin," "pigmentation," "granules," etc., of these elements, now found in the literature of the subject; Bevan Lewis's belief that neuroglia-cells are "lymph" channels, further sustain the view I advanced four years ago, viz., that while *neuroglia fibers are minutes capillaries* (which do not stain like ordinary vessels, owing to their covering) that carry plasma laden with oxidizing substance (adrenoxidase) to the neurons, their terminals in the latter being the neuro-fibrils which penetrate the cell-body by way of its dendrites, the *neuroglia-cells govern the quantity of this substance* admitted into the true nerve-"cells," *i.e.,* the neurons.

Interpreted from this standpoint, the wealth of neuroglia and neuroglia-cells in the posterior pituitary indicates, not that it is practically a useless and vestigial organ as Andriezen and others believe, but precisely the opposite, viz., that it is a *very highly differentiated organ.* This accounts for the fact that Berkley,[41] referring to the prevailing view that the true nervous elements almost entirely disappear in the neural lobe of the adult mammal, remarks, after examining about 2500 slides of this lobe: "After reading these statements, it was something of a surprise to find the above-described beautiful specimens of several types of ependymal neuroglia-cells, extending *from all portions of the middle and inferior regions of the cavity of the third ventricle.*" He also found in the posterior lobe itself, an array of nerve-cells of various types, some of which are very complex and evidently specific to the organ, being found nowhere else in the body. Many of these are reproduced and described in the first volume (opposite pages 495, 496 and 498).

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[38] Andriesen: *Loc. cit.*
[39] *Cf.* vol. i, pp. 539 to 590, incl.
[40] Andriesen: Intern. Monats. f. Anat. u. Physiol., vol. x, p. 532, 1893.
[41] Berkley: Brain, vol. xvii, p. 515, 1894.

It is not only the neuroglia-cells that communicate with the third ventricle, however. As stated above, each lobe is supplied with true nerve-fibers which connect it with the basal structures.

Several older anatomists, Sappey, Luschka, Müller, etc., refer to the presence of longitudinal nerves on the surface of the infundibulum, the pedicle of the pituitary, which nerves were found to extend up to the third ventricle; but it was only when the Golgi silver stain methods were introduced that this question could be studied satisfactorily.

Ramon y Cajal,[42] who studied the subject in the mouse, traced a direct communication between the basal tissues and the *anterior lobe.* In the basal tissues, the cell-bodies were found in a "*mass of gray matter behind the optic chiasm,*" *i.e.*, in the anterior extremity of the third ventricle, while their neuraxons passed downward towards the pituitary. Van Gehuchten[43] says in this connection, referring to Cajal's researches: "These fibers represent the axis-cylinders of a group of nerve-cells situated behind the optic chiasm. Several of these fibers end in the thickness of the pituitary's pedicle; others penetrate between the *epithelial cells* of the anterior or glandular portion of the pituitary." Berkley[44] also found nerves in this lobe, the fibers among the epithelial cells ending, as shown in the illustration opposite page 498 (vol. i, figure *l*) in the shape of small knobs. Andriezen's researches, as had those of Cajal, showed that the *anterior* lobe had "anatomical connection with the brain floor," and that the "development of a small *specialized* group of nerve-cells in the *basal* part of the brain cavity (thalamocoel) with which the subneural gland [the anterior lobe] came into relationship. The central canal of the spinal cord, traced forward into this region, was seen to undergo dilatation into a distinct ventricle." The far-reaching meaning of this statement asserts itself when it is recalled that Andriezen's researches include the whole of the animal scale from amphioxus, the lowest of vertebrates, to man. They indicate that simultaneously with the evolution of the *pituitary* there occurred not only that of the *special group of cells* intended to connect the organ with the base of the brain, but also that of *the third ventricle.*

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[42] Ramon y Cajal: Anales de la Soc. española de hist. nat., 2a Ser., vol. xxiii, p. 214, 1894.
[43] Van Gehuchten: "Anat. du système nerveux," vol. ii, p. 230, 1900,
[44] Berkley: *Loc. cit.*

Ramon y Cajal found that the *posterior* or *neural lobe* of the pituitary was filled with a close and thick plexus of fine varicose fibers, which ramified among the nerve-cells. Longitudinal sections showed that these fibers were "terminal arborizations of a bundle which passes *downward* into the infundibulum." Other fibers were observed to pass *upward* from the organ by way of its epithelial *walls* and to terminate in *a mass of gray matter* located behind the optic chiasm." "Downward" and "upward" obviously suggest the presence of sensory and motor paths to and from the neural lobe.

Of particular interest in this connection is a set of nerves shown to exist by Gentès.[45] This observer, who found that the partition between the two lobes contained a layer of cells histologically similar to the olfactory area—which layer I assimilate to the test organ—recently studied this structure anew with a view to tracing its connections. He was again led to the conclusion that it was an epithelial structure "in no way glandular and the nervous end-organs of which were sensitive or sensory," as to histological structure. In a still more recent study, Gentès[46] traced these connecting fibers from the sensory organ referred to, up to the tissues of the base of the brain. He says, in this connection: "Originating by free end-organs in the epithelial juxta-nervous layer [the sensory organ], they reach the sub-epithelial layer. They then *enter the neural lobe* and run through it in every direction. Following an *ascending direction* they go towards the organ's pedicle and soon form part of it; they can be followed up to the level of the *tuber cinereum,*" *i.e.,* the tissues that form the floor of the third ventricle.

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[45] Gentès: C. r. de la Soc. de biol., T. lv, p. 336, 1902.
[46] Gentès: *Ibid.*, p. 1560.

This affords a clear idea of the connection between the sensory structure (or test-organ) in the partition between the anterior lobe and how the impulses it awakens pass up to the third ventricle.

We thus have clearly defined paths from each pituitary body to tissues of the base of the brain: (1) the fibers from the anterior or glandular lobe communicating with the "mass of gray matter behind the optic chiasm;" (2) one set of fibers from the posterior or neural lobe communicating also with this mass of gray matter; and (3) the fibers from the neural lobe derived from the test-organ which pass up to the tuber cinereum forming the floor of the third ventricle.

The structures in the base of the brain with which the pituitary is connected by these nerve paths are themselves the source of large numbers of fibers, a large proportion of which pass posteriorly to the midbrain, a region which, as stated by Edinger,[47] is "occupied mostly with longitudinal bundles, tracts, and fasciculi to the spinal cord and to the cerebellum." This applies especially to the "mass of gray matter behind the optic chiasm" which receives fibers from both lobes—an important feature of the third ventricle in all vertebrates. Lying immediately above the infundibulum, and therefore just above the pituitary itself, it is termed by comparative anatomists, the "giant-celled supra-infundibular nucleus." In amphibians, reptiles and birds, it extends on each side of the ventricle, and fibers derived from it (the supra-infundibular decussation) project posteriorly, *i.e., towards the bulb.* In mammals, the supra-infundibular nucleus is likewise the starting-point of various bundles, *e.g.,* Meynert's commissure, for instance, which does not degenerate when the cortex is removed but the destination of which is unknown; Gudden's commissure, the fibers of which pass to the posterior corpora quadrigemina; the cerebellum, etc. It is also connected with structures anterior to it by motor and sensory fibers in Teleostei, as shown by Van Gehuchten recently. It projects two prominent bundles which spread out on the walls and floor of the third ventricle, thus contributing to the formation of the "central gray matter" of the base of the brain, a region which Foster[48] characterizes as "a bed for the development of the nuclei of the cranial nerves" and a continuation of the tegmental region, which he says "may perhaps be regarded as a more or less continuous column of gray matter, comparable to the gray matter of the spinal cord," and which "serves as *a sort of backbone to the rest of the central nervous system.*"

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[47] Edinger: "Anat. of Central Nerv. System," Amer. edition, p. 124, 1890.
[48] Foster: *Loc. cit.*, pp. 635 and 636.

The fibers traced by Gentès from the area of sensory cells—in the anterior pituitary which I assimilate to the "test organ" of lower forms—to the posterior lobe and thence to the tuber cinereum, are likewise merged with fibers which are projected to this "bed for the development of nuclei," since the tuber cinereum is necessarily traversed by fibers which Andriezen,[49] using the silver chromate method in fœtal and newborn kittens, traced *"directly from the posterior pituitary to far back towards the pons,"* which lies immediately above the medulla oblongata and contains the nuclei referred to. Whether originating from the anterior or posterior pituitary, therefore, the nerves which connect these organs with the base of the brain find therein both indirect and direct paths capable of transmitting their impulses to the spinal cord.*

Still, as is well known, the pons is a bridge for the passage of impulses, afferent and efferent, which travel between various parts of the nervous system, including the cerebrum. Motor impulses projected by the nerve paths from the pituitary should not only persist after removal of the brain (a fact already ascertained), but if the pituitary body is a motor center (as the effects of its removal indicate), removal of the structure above the mesencephalon (which contains the bed of nuclei and all pontine structures) quite beyond the crura cerebri which carry the impulses from the brain should, in the higher mammals (in which the fibers from the pituitary were traced), impair motility. Christiani[50] not only found this to be the case, the power of progression being annulled in the experimental animals (rabbits), but a phenomenon which promptly follows removal of the pituitary also appeared: tetanic spasm—due as we will see, to the accumulation of toxic wastes in the blood, the result in turn of impaired metabolism.

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*When I wrote the first volume, experimental stimulation of various parts of the cervical sympathetic by Cyon and others had led me to conclude that the impulses from the pituitary body to the adrenals passed down this nerve to reach the sympathetic chain below, and finally, the splanchnic. I have found since, however, that the nerves stimulated in the neck were branches which excited the thyroid gland and only indirectly, therefore, the adrenals. All the efferent nerves from either lobe of the pituitary body thus pass to the spinal cord.

[49] Andriezen: Brit. Med. Jour., Jan. 13, 1894.

[50] Christiani: Arch. f. Physiol., S. 465, 1894.

Another phenomenon which follows removal of the pituitary, we have seen, is hypothermia. Now, irritation of the structures of the third ventricle in the path of the nerves from the pituitary causes the opposite condition, hyperthermia. Isaac Ott, who, in 1884, began a series of studies having for their object to determine the location of heat-centers, found, among others, one located in the *anterior portion* of the *floor* of the third ventricle, and another in the *tuber cinereum.* The former region is precisely where all the fibers sent off posteriorly by the large gray nucleus to which Cajal traced afferent and efferent fibers from the anterior pituitary (a fact confirmed by Andriezen as to the presence of connecting fibers) originate, while the tuber cinereum contains those traced from the posterior lobe thereto by Gentès, and the fibers traced by Andriezen to the region of the pons. Ott and Harris[51] state that Ott's results were confirmed by von Tangl in the horse, and that the procedure mentioned causes a "great rise of temperature." These observations were also confirmed by Sakowitsch,[52] who found that puncture of the tuber cinereum raised both the *internal* and *peripheral* temperatures, the latter reached 43° C. (109.4° F.) six hours after the lesion was produced. Ott and Harris conclude that this is not due to division of fibers "coming from the corpus striatum, because a puncture through the mouth of the rabbit produces the same result, although only the lower surface of the *tuber* has been punctured with a needle."

This thermogenic function is evidently independent of the brain. "Fredericq[53] found," says Pembrey,[54] "that removal of the cerebral hemispheres in pigeons caused practically no difference in the daily curve of their rectal temperature. This observation has been confirmed by Corin and Van Beneden,[55] who have, in addition, shown that the pigeons without their cerebral hemispheres produce the same amount of carbon dioxide and heat as do normal pigeons. The rapid rise in temperature which occurs when a hibernating marmot awakens is not prevented by removal of the cerebral hemispheres." On the other hand, while the region punctured is clearly traversed by the fibers from the pituitary body, there is no organ anterior to it to give rise to thermogenic impulses. This affords additional evidence to the effect that the pituitary body is connected by nerve-paths with the spinal cord.

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[51] Ott and Harris: Therap. Gaz., June 15, 1903.
[52] Sakowitsch: Neurol. Centralbl., Bd. xvi, S. 520, 1897.
[53] Fredericq: Arch. de biol., T. iii. p. 747, 1882.
[54] Pembrey: Schäfer's "T. B. of Physiol.," vol. i, p. 864, 1898.
[55] Corin and Van Beneden: Arch. de biol., T. vii, p. 265, 1887.

This raises the question as to whether the areas punctured by Ott, von Tangl, Sakowitsch and others, can be considered at all as heat "centers." The fact that several such "centers" have been discovered suggests that the thermogenic impulses evoked are merely due to the irritation, *i.e.*, congestion of areas containing thermogenic nerve-paths. Schäfer[86] writes in this connection: "It is, however, very doubtful whether the facts observed warrant the assumption that the parts in question, which are apparently irritated by the lesion, are specific centers to determine the production of heat. For when the experiments on this subject are examined, it is found that the results are closely dependent upon the establishment of an irritative lesion in parts which are either directly in, or in close proximity to, the path taken by motor impulses." In view of the foregoing evidence this indicates that *the pituitary body is the general heat center*. I will adduce considerable additional evidence to this effect.

The fact that injuries or experimental lesions of the cortex, corpus striatum and crus cerebri can likewise cause a rise of temperature does not militate against this conclusion. They merely irritate areas that normally do not awaken thermogenic impulses but which, when artificially stimulated, do so by transmitting violent motor stimuli (*quasi* voluntary) to portions of the spinal system in which the nerve-paths of the thermogenic mechanism occur.

To poise these statements, and particularly the conclusion that the pituitary body is connected with the spinal system by nerve-paths on a solid foundation, however, it is necessary to show (1) that, irrespective of the brain, motor impulses can be provoked by irritating the paths of the nerves from the pituitary,

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[86] Schäfer: *Loc. cit.*, vol. ii, p. 717.

i.e., the walls and floor of the third ventricle, (2) that the pituitary body itself can likewise evoke motor phenomena, and (3) raise the temperature of the body at large. The first line of evidence will alone be considered in this section, the two others being considered in succeeding sections.

Flourens, Bechterew, Weber, Ferrier and others obtained muscular movements by exciting the walls of the third ventricle, which contain, we have seen, fibers from the gray nucleus connected by nerves with the pituitary. As these might be ascribed to the cortex through sensory impulses carried by the optic thalamus, they will not be taken into account. Magnan,[57] however, caused epileptic seizures *after* removing the hemispheres. Vulpian[58] was also led to conclude by experiments that the center for epileptic convulsions was located at the base of the brain. Ziehen[59] caused prolonged tetanic spasm in rabbits by irritating the basal tissues after removing both hemispheres. Hering[60] found it impossible to inhibit tonic spasm in 20 monkeys in which the pyramids had been severed, thus disconnecting what is generally believed to be the path for voluntary impulses to the spinal cord. Prus,[61] moreover, showed that after division of the pyramids, the spasmogenic impulses passed by way of the base, *e.g.*, the tegmentum and pons, and his results were confirmed by Bischoff,[62] Hering[63] and others. Finally, Nino Samaja[64] after an elaborate experimental study of the question concluded that in the higher mammals tonic spasms were "exclusively" due to impulses derived from the base of the brain. The most violent kinds of muscular contractions are readily produced, therefore, irrespective of any brain action, by stimulating structures that contain nerve-paths from the pituitary body. This evidence shows also why removal of the pituitary is followed by such marked muscular weakness and relaxation, and by hypothermia: as the general center of all vegetative functions it governs the heat mechanism, *i.e.*, general oxygenation, and thereby the intrinsic functions of the muscular system—as additional testimony will demonstrate.

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[57] Magnan: Arch. de physiol., T. v, No. 5, p. 115, 1873.
[58] Vulpian: C. r. de l'Acad. des sciences, Apr. 27, 1885.
[59] Ziehen: Deut. med. Woch., Bd. xiv, S. 604, 1888.
[60] Hering: Wiener klin. Woch., Nu. 33, S. 831, 1899.
[61] Prus: *Ibid.*, Bd. xi, S. 857, 1898.
[62] Bischoff: *Ibid.*, Nu. 39, S. 960, 1899.
[63] Hering: *Loc. cit.*
[64] Nino Samaja: Rev. Méd. de la Suisse Romande, Mar. 20, 1904.

Pending this evidence the following conclusions are submitted: *(1) the neural or posterior lobe of the pituitary body is not, as generally believed, a functionless organ, but a highly organized nerve-center containing several types of nerve-cells; (2) both lobes are connected with the overlying third ventricle by nerve-paths which, through nerves from the giant-cell supra-infundibular nucleus and in the tuber cinereum, extend posteriorly to the midbrain—a continuation of the spinal gray matter which contains the nuclei of the cranial nerves; (3) the nerves that connect the pituitary body with the spinal cord passing posteriorly in the gray substance of the walls and floor of the third ventricle, various experimental phenomena now ascribed to "centers" in these structures, are in reality due to irritation of these nerves and to the artificial production of manifestations normally evoked by the pituitary body as a motor and heat center.*

THE NEURAL LOBE OF THE PITUITARY AS THE SEAT OF THE SYMPATHETIC CENTER.

In many invertebrates, two ganglia preside over the entire nervous system, the supra- and sub-œsophageal. If in the snail, for example, as shown by Vulpian[65] the upper (cerebral) ganglion is removed, the animal lives several weeks, but it remains absolutely motionless. If, on the other hand, the inferior ganglion is removed, the animal dies within twenty-four hours. Again, galvanic excitation of the cerebral ganglion produces no appreciable effect; similar excitation of the lower ganglion, however, provokes violent muscular movements, and if prolonged, often "arrests the heart in dilatation and diastole as is the case when the pneumogastric is stimulated in the neck of vertebrates"—in other words, inhibits it. Now, physiologists teach, although as stated by Langley[66] they "are still far from any real knowledge of the processes involved in inhibition," that it is a physiological function, and that the slowing of the heart's action which attends stimulation of the vagus in the neck exemplifies the process. This is, in my opinion, a baneful conception; one indeed which has misled clinicians in their interpretation of several heart disorders and their treatment, and which, as I will show, has perpetuated our ignorance of the manner in which many of the most violent poisons cause death.

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[65] Vulpian: cited by Letourneau: "La Biologie." p. 389, 1891.
[66] Langley: Schäfer's "T. B. of Physiology," vol. ii, p. 674, 1900.

In the first volume I adduced evidence showing that the inhibitory phenomena and cardiac arrest caused by passing a current from the nose to the bulb were due to excitation of the pituitary body neural paths. In an article published since the first volume appeared[67] I emphasized the fact that inhibition was *not* a physiological function, and that it was due to a *morbid vasomotor constriction of the coronary arteries,* which slowed the heart because it deprived it of blood.

That the pituitary body contains a center capable of influencing the entire vascular system is demonstrable experimentally.

Cyon[68] observed, in the course of experiments, on a large number of animals (carried on to study the relations between the thyroid and the pituitary), that any pressure, even the slightest, upon the pituitary body at once gave rise to a sudden variation of the blood-pressure, and to a marked reduction in frequency of the heart beats. He then applied the electric current to the exposed pituitary and found that an extremely weak current produced the same effects but to a much more intense degree. Not only was the increase of vascular tension general, but the suddenness with which the pressure rose could only be caused by a sudden constriction of the arteries.

Cyon's observations have been fully confirmed recently by F. Masay[69] and amplified in such a manner as to locate distinctly in the pituitary body the origin of the phenomena witnessed. His investigations showed that mechanical and electrical excitation of this organ caused a marked and immediate rise of blood-pressure—from 81 mm. Hg. to 200 in one instance—and that this effect was not prevented by section of both vagi. After splitting the soft palate longitudinally, a delicate electric trephine was used to remove a disk of bone immediately beneath the pituitary body. Through this opening, two needle-like, perfectly insulated electrodes could easily be introduced. The variations of blood-pressure—the kymograph being connected with the carotid—and pulse-rate are clearly shown in the tables reproduced below. They indicate the comparative effects of excitation of the tissues around the opening, of the pituitary proper, and of the same organ after section of both vagi.

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[67] Sajous: N. Y. Med. Jour., May 14 and 21, 1904.

[68] Cyon: Archives de physiol., vol. x, p. 618, 1898.

[69] Masay: Ann. de la Soc. roy. des sci. méd. et nat. de Bruxelles, T. xii, Fasc. 3, 1903.

Exp. I.—Young Dog; Weight, 3.30 Kilog.	Blood-pressure.
Prior to excitation	63 mm. Hg.
Excitation of neighboring structures	63
After	63
Excitation of neighboring structures	63
After	63
Excitation of pituitary body	108
Immediately after	63
60 seconds after	63

Exp. V.—Dog; Weight, 2.6 Kilog.	
Prior to excitation	81 mm. Hg.
1st excitation of pituitary body	144
Immediately after	90
2d excitation of pituitary body,	
15 seconds	200
30 seconds	190
2 minutes	170
Immediately after	90

Exp. IX.—Dog; Weight, 5 Kilog.	
Both vagi cut.	
Prior to excitation	162 mm. Hg.
Excitation of pituitary body,	
first 15 seconds	280
second 15 seconds	270
Immediately after	225
1 minute later	156
2d excitation of pituitary body	252
" " " " " (close)	214
Immediately after	144
1 minute later	154

These striking effects speak for themselves. The blood-pressure was raised instantly, precisely as when the lower segment of the transected spinal cord is stimulated, in accord with Cyon's observation. Misled, however, by the prevailing view that the posterior lobe is a vestigial organ and the belief that the anterior lobe is a secreting gland, Masay attributed tentatively these effects to this "secretion." Not only, as I will show, is neither lobe of the pituitary a secretory organ, but it is evident that the rise of pressure throughout the whole organism could not have been produced instantaneously with the distribution of such a secretion as a preliminary feature of the process. As we will see presently, in fact, he produced similar effects by stimulating the medulla oblongata, with which, in the light of the facts submitted in the preceding section, the pituitary body is connected by nerve-paths.

This direct connection between the pituitary body and the bulbar centers accounts—in the light of my views—for an observation made by Masay, viz., that "during excitation [of the pituitary] the power of the heart beats is *diminished*, while immediately after, it increases very greatly and becomes greater than normal." We have here, in my opinion as previously stated, an example of *inhibition*, a *morbid process* due to excessive vasomotor contraction of the coronaries, as shown by the following evidence.

Brown-Séquard over fifty years ago[70] observed that stimulation of the lower end of the cut vagus, in the neck, caused *contraction* of the coronaries—a fact which led him to conclude that the vagus was the vasomotor nerve of the heart. In 1895, W. T. Porter[71] concluded that the vagus contained vasoconstrictors, a current of defibrinated blood passed at a constant pressure through the coronaries of an isolated heart being materially reduced in volume by excitation of this nerve. Maas[72] confirmed Porter's results. Heymans and Demoor[73] then found histologically that the muscular coat of the coronaries contained a rich network of vasomotor fibers. My own study of the subject showed that the cardio-inhibitory impulses transmitted to these vessels by the vasoconstrictor fibers *in* the vagus were derived from the *vasomotor center*.

A phenomenon, the mechanism of which had never been explained, *i.e.*, cardiac inhibition, thus readily accounts for the diminished cardiac action noted by Masay on stimulating the pituitary body. He produced an effect identical to that obtained by the brothers Weber[74] when, in 1846, they passed a current from the intranasal surfaces to the spinal cord, viz., he inhibited its action by reducing the caliber of the coronaries and reducing the quantity of blood supplied to the heart-walls.

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[70] Brown-Séquard: "Experimental Researches Applied to Physiology and Pathology," New York, London, Paris, 1853.

[71] W. T. Porter: Boston Med. and Surg. Jour., Jan. 9, 1895.

[72] Maas: Pflüger's Archiv, Bd. lxxiv, Hft. 7 u. 8, S. 281, 1899.

[73] Heymans and Demoor: Mémoires de l'Acad. roy. de méd. de Belgique, T. xiii, 8me Fasc., 1895.

[74] Weber Brothers: "Handworterbuch d. Physiologie," Bd. ii, S. 42, 1846.

The inhibitory effect of excessive constriction of the coronaries has been demonstrated by several investigators. Chirac[75] found that the beats of a dog's heart were soon arrested when one of the coronaries was tied. Erichsen[76] observed a similar result after tying these vessels. Leonard Hill,[77] referring to the investigations of Cohnheim and Schulthess-Rechberg,[78] McWilliam,[79] Bettelheim,[80] and others, also states that "ligaturing one of the largest branches only is frequently sufficient to cause arrest." Again, Sée, Bochefontaine and Roussy[81] observed that substances capable of plugging the coronaries—lycopodium spores, for instance—also caused cardiac arrest. Porter[82] plugged the left coronary artery in nineteen dogs and says that "the closure of the artery was always promptly followed by arrest." As the result of closure by ligation in sixty-seven dogs, he reached the deduction that "the frequency of arrest is in proportion to the size of the artery ligated." As cardio-inhibitory impulses transmitted through the vasoconstrictors of both vagal trunks probably influence *all* the coronary vessels simultaneously, the ease with which the heart's action can be arrested by exciting the bulbar center is easily accounted for. Finally, Kolster,[83] Porter,[84] and others have shown experimentally that the part of the heart supplied by an infarcted coronary artery degenerates.

Yet, if the vasomotor impulses inhibit the heart by causing excessive constriction of the coronaries, the effects on the heart wall should coincide with those resulting from deprivation of blood. Such is undoubtedly the case: E. Weber[85] observed that during partial inhibition the cardiac contractions were weakened, while Schiff[86] found that the muscular elements of the entire organ responded less or not at all to stimuli. François-Frank, Fischel,[87] and others observed that the cardiac walls were softer than usual. Foster[88] states that when the interrupted current is used to stimulate the vagal trunk, the heart remains in diastole, motionless and flaccid. When, however, the current is weak, the beats are only slowed and weakened. Coats[89] ascertained manometrically that the contractions were markedly reduced in force. Gaskell[90] and Stefani[91] found that the ventricular tonicity was reduced. Muskens[92] also found that stimulation of the vagus lessened the force of the contraction in the frog.

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[75] Chirac: "De Motu Cordis," p. 121, 1698.
[76] Erichsen: London Hospital Gazette, vol. ii, p. 561, 1842.
[77] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 1, 1900.
[78] Cohnheim and Schulthess-Rechberg: Virchow's Archiv, Bd. lxxxv, Hft. 2, S. 503, 1881.
[79] McWilliam: Jour. of Physiol., Vol. viii., p. 296, 1887.
[80] Bettelheim: Zeitsch. f. klin. Med., Bd. xx, S. 436, 1892.
[81] Sée, Bochefontaine and Roussy: C. r. de l'Acad. des sci., T. xcii, p. 86, 1881.
[82] Porter: Jour. of Exper. Med., vol. i, p. 46, 1896.
[83] Kolster: Skandinav. Archiv f. Physiol., Bd. iv, S: 1, 1893.
[84] Porter: Pflüger's Archiv, Bd. iv, S. 366, 1893.
[85] E. Weber: *Loc. cit.*
[86] Schiff: Archiv f. physiol. Heilk., 9ter Jahrgang, S. 22, 1850-51.

Gaskell[93] characterizes as "most striking" the attending *depression of activity.* Still, there is no loss of inherent muscular irritability, since, according to Foster,[94] a pin prick in the heart during inhibition may cause a beat; the morbid phenomena are, therefore, the result of a deficient supply of the nutrient components of the blood. Porter[95] states that "but little is known as to the constituents of the blood which are essential to the life of the mammalian heart," and that "an abundant supply of oxygen is certainly highly important." The manner in which the deficiency of these blood constituents causes the inhibitory effects is suggested in the following lines of Langley's:[96] "The decrease of rigidity in the inhibited muscular tissue shows that inhibition is not caused by the development of a contractile force, acting in a direction opposed to the normal one and overpowering it. We are then brought to the conclusion that certain nerve impulses—the inhibitory nerve impulses—are able to *lessen* or to *stop* the chemical change *in the tissue* which leads to contraction."

It is evident, therefore, that even the diminution of the heart-beats which Masay observed *during* excitation is likewise due to vasomotor constriction.

Any doubt that may remain as to the influence of stimulation of the pituitary body on the vascular system is removed by the fact that all of Masay's experiments indicate (1) that the rise of the blood-pressure and pulse occurred concurrently and fluctuated with the mechanical or electrical excitations of the exposed pituitary, and (2) that the recession of pressure, *i.e.*, the resumption by the arteries of their former caliber, occurred immediately after each excitation ceased. The following table illustrates forcibly the suddenness of the fluctuations under the influence of excitation:

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[87] Fischel: Archiv f. exp. Path. u. Pharm., Bd. xxxviii, Hft. 3 u. 4, S. 228, 1897.

[88] Foster: "T. B. of Physiol.," sixth Amer. edition, Phila., 1895.

[89] Coats: Bericht d. k. Sachs. Gesellsch. d. Wissensch., S. 360, 1869.

[90] Gaskell: Philosoph. Trans., p. 1019, 1882.

[91] Stefani: Archives ital. de biol., T. xxiii, p. 172, 1895.

[92] Muskens: Pflüger's Archiv, Bd. lxvi, Hft. 5 u. 6, S. 328, 1897.

[93] Gaskell: Schäfer's "T. B. of Physiol.," vol. ii, p. 169, 1900.

[94] Foster: "T. B. of Physiol.," sixth Amer. edition, 1895.

[95] Porter: "Amer. T. B. of Physiol.," vol. i, second edition, p. 143, 1900.

[96] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 674, 1900.

Exp. IV.—Dog; Weight, 3.8 Kilog.	Blood-pressure.
Prior to excitation	81 mm. Hg.
Mechanical excitation of pituitary	98
Immediately after	36
Electrical excitation	100
Immediately after	72
Electrical excitation	100
Immediately after	72
Electrical excitation	100
Immediately after	81

This sudden elevation of pressure whenever the organ was stimulated occurred repeatedly until a clot prevented further work. An additional feature of these results is that the animal had been given morphine and curare, so that the rise in pressure represents an excess over that already caused by these drugs. Were it not for this, the difference between the pressure before and during excitation would have been much greater.

Still, if Masay actually inhibited the heart when he observed that excitation of the pituitary diminished cardiac power, and the brothers Weber produced the same effect by passing a current from the nasal mucous membrane posteriorly, removal of the pituitary body should prevent the phenomena caused by nasal excitation. Cyon[97] found that the inhibitory slowing of the heart obtained by stimulating the nasal mucous membrane and the reflex phenomena caused by the same procedure could no longer be obtained immediately after extirpation of the pituitary body. Even the most active stimulants, ammonia, for instance, applied directly to the nasal mucous membrane, failed to elicit the least response. "The beneficial influence of reflex action on the heart obtained by stimulating the nasal mucous membrane in *syncope*," says this physiologist, "must react, therefore, indirectly upon the cardiac nerves through the intermediary of the pituitary body"[88]—a true statement when, in the light of my views, the reflex effect is ascribed to constriction of the cardiac arteries, which are dilated (their muscular layer as well as the skeletal muscles being relaxed) during syncope.

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[97] Cyon: Archiv f. d. ges. Physiol., Bd. lxxi, S. 431; and Bd. lxxii, S. 635, 1898.

This beneficial action of reflex contraction of the coronaries exemplifies clearly how the heart may be inhibited. In syncope the dilated vessels are restored to their normal caliber; in inhibition, excitation decreases their caliber until the streams of blood supplied to the heart are totally inadequate to sustain the functional activity of the organ. *Experimental inhibition, therefore, is an artificial process and does not, as physiologists teach, exemplify a normal function.*

All this has served further to show, not only that the coronaries are supplied with vasomotor nerves, but also that the pituitary body is *a* vasomotor center. Indeed, the latter feature, and the fact that, as believed by Masay, it is not a problematical secretion which causes the rise of blood-pressure, are placed on a solid basis by the experimental demonstration that stimulation of the pituitary body and of the bulbar vasomotor center produce similar effects. This is brought out in two of Masay's tables. The conditions presented here are such as to insure as much as possible correspondence in the strength of current used, the duration of stimulation, etc.

EXP. V.—DOG; WEIGHT, 2.6 KILOG.	Blood-pressure.
Prior to excitation	81 mm. Hg.
1st excit. of pituitary body	144
2d " " " "	
first 15 seconds	200
after 30 "	190

EXP. II.—DOG; WEIGHT. 5.5 KILOG.	
Prior to excitation	90
1st excit. of bulb	136
1st " " " after 30 seconds	154
2d " " " " " "	126

The needle-electrodes were merely thrust into the medulla oblongata from the front, instead of into the pituitary. The recession of the blood-pressure after stimulation was immediate in both instances, thus showing that the region stimulated in the bulb was *a* vasomotor center.

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[88] Richet's "Diction. de physiol.," vol. iv, p. 131, 1900.

All this evidence emphasizes another fact, viz., that among the paths from the pituitary body to the spinal cord referred to in the preceding section, there are fibers that are capable of conducting vasomotor impulses at least as potent in their influence upon the general vascular system as those transmitted along the familiar paths of the spinal cord by the bulbar centers. That the impulses derived from the pituitary reach the peripheral vessels by way of the bulb and its spinal vasomotor pathways is self-evident, since there is no ground for the assumption that the pituitary body has an autonomous set of fibers for this purpose.

The presence of such an autonomous set of vasomotor fibers between the posterior pituitary and the bulbar vasomotor center, however, recalls vividly the relationship of the spinal cord below the bulb with the great sympathetic, and suggests an important question: may the vasomotor impulses not be sympathetic as to their distribution? Excitation of the bulbar vasomotor center causes, as stated by Winfield S. Hall, "general contraction of all the arteries," while paralysis of this center "causes *general* dilatation." Sympathetic vasomotor action, on the other hand, is a restricted one; thus, Howell, after showing the influence of stimulation and section of sympathetic paths, writes: "From these and numerous similar experiments, we may conclude that normally the arteries—*that is, the arterioles*—are kept in a condition of tone by impulses received through the vasoconstrictor fibers,"—evidently sympathetic constrictors. Now, the manner in which Masay's results could have been awakened through sympathetic fibers from the posterior lobe to the bulbar vasomotor center, and thence down the cord to the origin of the sympathetic nerves, the ultimate nerve-path to the tissues, is suggested by another quotation from Howell's work: "When vasoconstrictor fibers are stimulated, there is a *rise of pressure* in the artery supplying the organ and a fall of pressure in the veins emerging from the organ. This result is what we should expect if the constriction takes place in the region of the *arterioles*." As these terminal vessels are governed by sympathetic fibers, stimulation of the pituitary must either have raised the pressure by constricting the arterioles through these fibers, or by stimulating the bulbar vasomotor center, thus causing constriction of all arteries. Which of the two processes is the true one?

Experimental evidence shows clearly that it cannot have been merely because the impulses excited the vasomotor center. As is well known, Ludwig and Owsjannikow, who established the limits of the latter, found that when the midbrain *above* the bulb was cut through, the blood-pressure was not materially influenced, and that it was only when the bulb was cut across or below the now recognized location of the center that paralysis of the vessels was complete. It is evident, therefore, that the vasomotor center is not located above the bulb.

Such is not the case, however, with what I will hereafter designate as the "sympathetic center."

In the twentieth chapter I will submit evidence to the effect that antipyrin and other coal-tar products and drugs produce their antipyretic and analgesic effects precisely by causing constriction of the arterioles supplied with the sympathetic vasoconstrictors to which Howell refers. Now, Sawadowski[98a] found that when the tissues of the base of the brain were cut through, "the cut being made through the thalami optici or the corpora striata," antipyrin and other antipyretics were no longer active. The section being far above the bulb, though immediately below the pituitary body, the fibers severed were those which transmitted Masay's blood-pressure raising impulses. The fact that these sympathetic vasoconstrictor fibers influence only the arterioles, the smallest arteries, explains also why Ludwig and Owsjannikow did not affect the vascular tension markedly by dividing the same nerves.

Again, the basal structures severed by Sawadowski—at least the walls of the third ventricle to which Cajal, Van Gehuchten and others have traced nerve-fibers from the pituitary—give passage to typical sympathetic fibers. Referring to this region, Edinger[98b] says: "The inner side of the thalamus is separated from the ventricle by a uniform layer of gray matter. This is called the central gray matter of the middle (third) ventricle, and consists of a tissue rich in cells, and traversed in all directions by numerous *fine, medullated* nerve-fibers." Now, the identity of such fibers is well known. "A striking feature of the *sympathetic* system," says Langley,[983] "is the predominance of *small medullated* fibers in it. This was pointed out by Bidder and Volkmann in 1842. The great majority of its medullated fibers vary from 2μ to 3.5μ in diameter. . . . . . Very large medullated fibers, 15 to 20μ, which are common in the roots of the spinal nerves, do not occur in the sympathetic system." Kölliker[984] also teaches that "the neuraxes of sympathetic neurons become invested in many cases with a thin medullary sheath, thus forming very fine medullated fibers, which, on account of their small size, can be differentiated from the smallest cerebro-spinal fibers."

[98a] Sawadowski: Centralbl. f. d. med. Wissen., Jahrgang xxvi, pp. 145, 161, 1888.

[98b] Edinger: "Anat. of Central Nerv. System," American edition, p. 260, 1899.

Cyon and Masay, in the light of this evidence, therefore, stimulated the *sympathetic center*, the marked elevation of blood-pressure provoked (and which receded instantly when the excitation ceased) being due to *constriction of all the arterioles* and the resulting accumulation and pressure behind the vascular obstruction.

This obviously liberates the bulbar vasomotor center of the functions ascribed to the sympathetic system, and endows the latter with autonomous functions. That such is the case is sustained not only by the foregoing evidence, but also by the anomalous rôle which the bulbar vasomotor center is inferentially made to play according to prevailing teachings (in view of the fact that experimental work on the sympathetic is used to exemplify vasomotor action, constriction and dilation) not only as the regulator of vascular tonus, but also, through its connection with the sympathetic, of functions of different kinds, secretory, motor (peristalsis) and inhibitory. Although, as will be shown in the twentieth chapter, the latter are, in reality, nothing but what might be termed "experimental" pseudo-functions, the fact remains that as stated by Hall in reference to the sympathetic system: "The importance of this system in the control of the vital functions of the body can hardly be overestimated." That it should be provided with its own center—though closely related with bulbar vasomotor center through its fibers thereto, which, as we have seen, are of the special sympathetic type—is, therefore, only logical.

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[983] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 648, 1900.
[984] Kölliker: Cited by Huber: Jour. of Compar. Anat., Sept., 1897.

This involves the conclusion that the large vessels, as well as the arterioles, are supplied with vasomotor nerves, the former being governed by the bulbar vasomotor center. This is in accord with the more recent teachings of histology. Joris,[98a] in a comprehensive review of the subject, and after considerable histological work, using the Golgi and Ehrlich methods, concludes with the remarks: "A fact which we must consider as established is that all arteries and all veins are provided with intrinsic nerves. Their existence in the nerve-centers is not as yet established, notwithstanding the researches of Obersteiner, Morisson and Huber. But these negative results depend certainly upon the technical difficulties." To emphasize his statements, Professor Joris adds: "I said intentionally all the *arteries* and all the *veins*" . . . . . "blood-vessels are supplied with nerves, because their walls contain muscle-fibers." This can also be said of veins, among which he enumerates, besides the smaller veins, the "venæ cavæ, jugulars, iliacs, etc."

As to the distribution of these nerves and their function, Joris writes: "All the nervous branches which surround and accompany the blood-vessels do not ramify in the thickness of their walls. Many of them follow only momentarily the path of the vessels and terminate in other organs. These are the satellite nerves. The true vascular nerves are quite distinct from the satellite nerves." . . . . . "These [true vascular] nerves form, by their anastomoses, a perivascular plexus. Finer branches, differing structurally and having different functions, emanate from this plexus. Some are destined for the smooth fibers of the tunica media (*motor fibers*); the others are sensory (*sensitive fibers*)." All these nerves are evidently vasomotor, since they "end absolutely in the thickness of the vascular walls. Their anastomoses are mutual and never with neighboring nerves, muscular, glandular, etc." . . . . . "The perivascular plexus is clearly isolated; the aggregate of fibers which compose it form an independent exclusively vascular apparatus." As to the sensitive fibers, "they sink into the depth of the tunica adventitia as do the motor fibers, but do not anastomose with them."

[98a] Joris: Bull. de l'Acad. roy. de med. de Belgique, iv série, T. xx, p. 502, 1906.

If, as I hold, the larger vessels are governed by the vasomotor (bulbar) center, while the arterioles are controlled by the sympathetic (posterior pituitary) center, the nerves supplied to the latter vessels should be those of the sympathetic type, *i.e.*, the fibers of Remak, the small, supposedly "nonmedullated" fibers referred to a few pages back: "Vascular nerves are formed of nonmedullated and medullated fibers," writes Joris; "the latter are numerous on the surface of the vessels, the caliber of which exceeds 80 microns. They become gradually more scarce, and disappear completely along the more delicate vessels. None but nonmedullated fibers remain when the caliber of the vessel is approximately 50 microns." This diminutive size is quite compatible with the anatomical relationship of the arterioles as I interpret this term, *viz.*, the more or less elongated terminals of all arteries—which open directly into the capillaries, including the so-called "precapillary vessels.

The location of the neural lobe of the pituitary at the head of the spinal structures that project into the base of the brain; its identity as a highly differentiated structure; and the fact that in a large group of animals, either as the "sub-œsophageal ganglion" of various invertebrates, or as the "central ganglion" of the lower chordata, it is the general center of the nervous system, and the experimental evidence submitted clearly points to this organ as the seat of a center, such as the sympathetic center, which, as I will show, takes part in a function which far exceeds in importance that of preserving the vascular tonus—the only rôle fulfilled by the bulbar vasomotor center.

Summarized, all this evidence seems to me to have shown: (1) *that the neural or posterior lobe of the pituitary body contains a center which governs the great sympathetic system, including its vasoconstrictor nerves to the arterioles;* (2) *that this center is connected by nerve-paths with the medulla oblongata and spinal cord through which it transmits its impulses;* (3) *that the bulbar vasomotor center does not maintain the tonus of the arterioles, as now taught, but solely that of the veins and larger arteries;* (4) *that the center in the posterior or neural lobe of the pituitary which governs the caliber of the arterioles, should be termed the "sympathetic center."*

THE NEURAL LOBE OF THE PITUITARY AS THE SEAT OF COMMON SENSIBILITY AND AS A GENERAL MOTOR CENTER.

The pituitary body remained whole, of course, in the decerebrated animals referred to in a foregoing section, and the paths to the spinal cord likewise. Foster,[99] referring to such animals, states that they "may be kept alive *and in good health* for a long time," and they exhibit "a spontaneity obviously betokening the possession, not merely of a *conscious volition*, but of a certain amount of *intelligence*." Now, there is no structure in the base of the brain that is endowed with such an attribute. The optic thalami and corpora striati are the only organs to which such an important rôle might hypothetically be ascribed; but we have seen that in Goltz's dog, destruction of these organs did not prevent its remaining "alive and in good health for a long time," and that all its functions were performed normally. The posterior pituitary alone is capable of playing such a rôle: not only does it contain highly differentiated nervous elements, various types of highly organized nerve-cells, but even its outer layer was found by Luschka,[100] Müller,[101] who studied the pituitary from myxine to man, and others, to be composed of gray substance recalling that of the cerebral cortex.

The neural lobe thus presents structural features which indicate that it is fully able to carry on functions of the highest order, and in which co-ordination is blended with enough conscious volition to account for the manifestations of intelligence to which Foster refers. As we will now see, it can not only generate motor impulses, but also receive sensory impulses and impressions—the products of sensual perceptions—of various kinds, and co-ordinate a group of motor impulses adapted to the needs of the moment—not mere manifestations of reflex action, but complex combinations. Even this represents but a refinement of functions which the neural lobe alone governs in the primitive chordata. Thus Loeb[102] states that Ferrier "mentions the one ganglion of the Ascidians as illustrative of the ganglion reflexes," *i.e.*, of a structure capable of receiving sensory impulses and sending forth motor stimuli.

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[99] Foster: *Loc. cit.*, p. 643.
[100] Luschka: "Der Hirnanhang und die Steidrüse des Menschens," 1860.
[101] Müller: Jenaische Zeit. f. Naturw. Bd. vii, S. 327, 1873.
[102] Loeb: *Loc. cit.*

The identity of the pituitary body as a sensory center is emphasized first of all by the fact that lesions of the cortex do not influence general sensibility.

"Innumerable cases have been reported of lesions of the motor cortex," writes C. K. Mills,[103] "without the slightest impairment of sensibility. In several cases of excision of the human cortex in the Rolandic region by surgical operations, careful studies of the patients by the writer and others failed to show any impairment of sensation." As we all know, a large number of cases of extensive injury of the cerebrum fully sustain this assertion by the absence of sensory phenomena. Again, Charcot and Pitres[104] state that "the paralyses of cortical origin are accompanied sometimes with disorders of cutaneous or muscular sensibility, but these sensory disorders, which are eventually associated with motor paralyses, do not show a *direct* or *necessary* connection with lesions of the motor zone." We have seen also, that the pigeon deprived of its hemispheres can feel and shake off a fly that chances to alight on the feathers of its head; that Goltz's dog, similarly mutilated, reacted promptly to tactile sensation, limped when hurt, promptly raised its feet when these were placed in cold water, etc. On the other hand, Schäfer[105] concludes a comprehensive review of the question with the remark: "This no doubt lands us in the unsatisfactory position that we are unable certainly to say in what part we are to localize cutaneous sensibility, or even *if it is localized at all in the cortex.*"

This obviously suggests that the posterior pituitary, *i.e.*, the neural lobe, might in the light of my views, fulfill this function. Yet, a decapitated frog, *i.e.*, one deprived of its basal ganglia and part of the central gray matter, and, therefore, of the pituitary body, will raise one of its limbs and adjust it to a spot upon which some irritant has been placed in order to rub it. We must not lose sight of the fact, however, that *all* protoplasm is endowed with reflex attributes and that nerve impulses only *multiply* their inherent properties. We have in this auto-protective motion of the decapitated frog, therefore, but an expression of its latent capabilities. As stated by Foster,[107] "the phenomena presented by a frog possessing the middle portions of the brain differ widely from those presented by a frog possessing a spinal cord only. We may, perhaps, broadly describe the behavior of a frog from whom the cerebral hemispheres only have been removed by saying that such an animal, though exhibiting no spontaneous movements, can, by the application of appropriate stimuli, be induced to perform all, or nearly all, the movements which an entire frog is capable of executing." Of the frog possessed of its spinal cord only, he says: "When placed on its back it makes no attempt to regain its normal posture; in fact, it may be said to have completely lost its normal posture, for when placed on its belly it does not stand with its fore feet erect, as does the other animal, but lies flat on the ground. When thrown into water, instead of swimming it sinks like a lump of lead. When pinched or otherwise stimulated it does not crawl or leap forward; it simply throws out its limbs in various ways. When its flanks are stroked it does not croak; and when a board on which it is placed is inclined sufficiently to displace its center of gravity it makes no effort to regain its balance, but falls off the board like a lifeless mass. Though, as we have seen, the various parts of the spinal cord of the frog contain a large amount of co-ordinating machinery, so that the brainless frog may, by appropriate stimuli, be made to execute various purposeful co-ordinate movements, yet these are very limited compared with those which can be similarly carried out by a frog possessing the middle and lower parts of the brain in addition to the spinal cord." The author also states that "the phenomena presented by animals deprived of their cerebral hemispheres show that this machinery of co-ordination is supplied by cerebral structures lying between the cerebral hemisphere above and the top of the spinal cord below," and subsequently refers to the "foundation of the machinery in question" as "the tegmental region *from the bulb upward*." The tegmental region, that through which ascends the *fillet*, is likewise referred to by Foster[108] as a "probable path of sensations of one kind or another from *the body at large*."

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[103] C. K. Mills: "The Nervous System and its Diseases," Phila., 1898.

[104] Charcot and Pitres: "Les centres moteurs corticaux chez l'homme," Paris, 1895.

[105] Schäfer: "T. B. of Physiol.," vol. II, p. 728, 1900.

[106] Schäfer: *Ibid.*, vol. II, p. 768.

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[107] Foster: *Loc. cit.*, p. 637.

The neural lobe may well be, therefore, the organ in which, repeating Schäfer's words, we can "localize cutaneous sensibility" and in fact sensory impulses received from mucous membranes, muscles, etc., since in Goltz's dog all functions, digestion, salivation, urination, etc., which involve reflex actions, were performed normally. As stated in the preceding section, moreover, this lobe is the only organ "lying between the cerebral hemisphere above and the top of the spinal cord below," as Foster says, that is capable structurally of carrying on the functions of a center. Finally, that it is actually the seat of sensibility is clearly suggested by the presence of various disorders of sensation when the pituitary body is diseased.

In acromegaly, for example, very severe headache of a neuralgic type is commonly observed. It is usually limited to the head but may extend over the entire body, as in a case reported by Hymanson,[109] or be localized, as in that observed by Pirie, who specifies "the face, chest, back and loins." The facial neuralgia is essentially within the domain of the fifth pair as emphasized by Gubler.[110] Rosenhaupt[111] found that when this characteristic pain was present, the skin of the face was hypersensitive. Breton and Michaut[112] noted that pressure on the points of exit of the fifth caused intense pain, with typical signs of acromegaly. In one of M. Allen Starr's cases[113] the pain was agonizing and was constant over the forehead and back of the eyes. In another instance, recorded by O. T. Osborne,[114] the pain is stated by him to have been "directly over the pituitary body" while the autopsy "revealed a plate of bone making pressure at this very point."

Disorders of sensibility of other kinds may likewise occur. Paræsthesia of the lower extremities and back was observed by Pearce Bailey[115] in a case of tumor of the pituitary, in which this organ was found, after death, to have been the seat of an extensive hæmorrhage. In his case of acromegaly, Pirie noted "shooting pains in combination with paræsthesia, tingling and numbness" of the arms and legs, and "a remarkable perversion of thermic sensibility" in the lower limbs, front of the abdomen and chest to about the level of the fourth rib, the patient having "no sensation of heat in these regions," and he refers to Sternberg as remarking "particularly on the occurrence of pain and paræsthesia as valuable signs for diagnosis in the *early* stages of the disease." Many similar instances could be quoted.

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[108] Foster: *Loc. cit.*, p. 716.
[109] Hymanson: Med. Record, July 1, 1899.
[110] Gubler: Correspondenzblatt f. d. Schweizer Aerzte, Dec. 15, 1900.
[111] Rosenhaupt: Berl. klin. Woch., Sept. 28, S. 893, 1903.
[112] Breton and Michaut: Gaz. des Hôpitaux, Dec. 13, 1900.
[113] M. Allen Starr: Med. Record, Feb. 3, 1900.
[114] O. T. Osborne: *Ibid.*, Mar. 4, 1899.
[115] Pearce Bailey: *Ibid.*, Apr. 16, 1898.

This is strikingly controlled by the fact that removal of the pituitary abolishes sensation even of the most sensitive nerve of the body, the fifth pair. Thus Cyon not only observed in the course of his investigations in a very large number of animals (though working in different lines) that removal of the pituitary annulled nasal sensory phenomena, sneezing, etc., but he also specifies[116] that all the nerves, *including the fifth* and glossopharyngeus, "lost their *reflex* influence after the pituitary body had been removed." The inference is obvious in view of the fact that section of the fifth deprives the nasal surfaces of sensibility. Whether severed between the nasal surfaces and the bulb, or between the latter and the pituitary body or destroyed along with the latter amounts to the same thing: we are brought to the inevitable conclusion that the fifth is also under the domain of the pituitary body—a fact which in turn explains why lesions of this organ can provoke sensory phenomena throughout the entire organism, for the fifth is but a portion of the great system of common sensation.

All these phenomena belong, however, to the domain of *common sensibility*. Do other special senses show evidence of being related in any way with the pituitary body?

Smell is sometimes impaired and even lost in acromegaly, as shown by cases reported by Joffroy,[117] Leszynsky,[118] Roxburgh and Collis,[119] and others. A study of the question—the details of which I will not inflict upon the reader—showed that the sense of olfaction *per se* could be influenced indirectly, the morbid effects being due to ischæmia and impaired nutrition of the olfactory area through involvement of the sympathetic center in the neural lobe. Another source of disorder in the nasal cavities is brought about through the sensory fibers of the mucous membrane. As stated by Haycraft,[130] "the fifth is the nerve of common sensibility to the nose, and in the case of disease or *section* of this nerve, irritants such as pepper, chlorine, and ammonia, produce no irritating effect." This statement is suggestive in view of the fact that removal of the pituitary body by Cyon produced, we have seen, identically the same effect.

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[116] Cyon: Richert's "Diction. de physiol.," vol. iv, p. 131, 1900.
[117] Joffroy: Le progrès médical, Feb. 26, p. 129, 1898.
[118] Leszynsky: Med. Record, Mar. 4, 1899.
[119] Roxburgh and Collis: Brit. Med. Jour., July 11, 1896.

While there is no ground for the conclusion that the pituitary body receives odoriferous impressions as far as available evidence is concerned, therefore, the common sensibility impressions are clearly referable to this organ.

Vision is impaired in a large proportion of cases of acromegaly—91 times in 174 cases according to Hertel[131]—and blindness is a frequent result. Optic nerve disorders are, at least in part, ascribable to pressure of the enlarged organ on the optic chiasm. Bi-temporal or one-sided temporal hemianopsia for form and color is also observed. The symptoms may appear early and follow a progressive course; conversely, the disease may have existed many years before visual disturbance appears. As shown by the statistics of Hertel, they may not appear at all, though the typical symptoms of acromegaly be present. In such a case, reported by Ferree Witmer[132] for instance, the eyes were examined by W. Campbell Posey. "As a result of the ophthalmological examination," says the latter, "it is evident that there is no pressure anywhere on the optic tract." Interesting in this connection, is the fact that among the symptoms recorded in this case was a "marked reduction of the common sensibility" and that "the sensibility of the fauces was also considerably diminished." In another case of acromegaly observed by Packard and Cattell, reported by Spiller,[133] "the visible fields for form and color were normal; the pupils responded freely to light in accommodation and in convergence" and yet common sensibility was markedly reduced. Thus tests to determine the rate of sense perception showed "a retardation of reaction time to forty per cent. below the normal." At the autopsy a round-celled sarcoma about the size of an English walnut was found in the pituitary body which pressed upon the optic nerves.

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[130] Haycraft: Schäfer's "T. B. of Physiol.," vol. ii, p. 1247, 1900.
[131] Hertel: Archives f. Ophthal., Bd. xli, Abt. i, S. 187, 1895.
[132] Ferree Witmer: Intern. Med. Mag., Jan., 1896.
[133] Spiller: Jour of Nerv. and Mental Dis., Jan., 1898.

Apart from the impressions of common sensibility, the anatomical connections of the visual tract do not present features which suggest a direct functional connection with the pituitary body. Indeed, Goltz's dog, though sensitive to a bright light, could not actually see. This does not apply of course to the oculo-motor muscles which in common with other muscles, are also related through the bulb, with the latter. Hence the strabismus often observed in acromegaly and neoplasms of the pituitary.

We are again brought to conclude, therefore, as far as the main functions of the eye are concerned, motion and common sensibility are the only ones related directly with the pituitary body.

Hearing is occasionally impaired in acromegaly, but a feature which stands out prominently in this connection is that disorders of sensibility appear always to be present concurrently—even when the very frequently observed symptom, tinnitus, fails to appear. In Pirie's case, for example, tinnitus accompanied the marked sensory disturbances to which reference has been made. In Hymanson's it also coincided with numbness of the hands. In Lackey's[124] tinnitus and impairment of hearing occurred in conjunction with numbness of both feet and hands. Deafness may also appear along with cutaneous hyperæsthesia as in Breton and Michaut's case. Conversely, Gibson states that his patient "was not at all deaf" and that "ordinary sensibility to touch, pain, heat, cold and electric stimuli was intact;" in Grinker's[125] case the special senses were normal and "the pain, touch and temperature senses" likewise. All these phenomena are readily accounted for by the fact that aside from the auditory nerve distributed to the cochlea, the vestibule and semicircular canals, the membrana tympani receives fibers from the fifth pair. "Although the innervation of the membrana tympani has not been conclusively established," write McKendrick and Gray,[126] "there is little doubt it is supplied with sensory nerves by the fifth, and also by the tympanic plexus, formed by fibers derived from the otic ganglion, from the petrosal ganglion of the glosso-pharyngeal, and from the carotid plexus." The aural symptoms of acromegaly, therefore, are not preversions of the sense of hearing, but disorders of general sensibility.

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[124] Lackey: Phila. Med. Jour., July 22, 1899.

[125] Grinker: Chicago Med. Recorder, Dec., 1903.

[126] McKendrick and Gray: Schäfer's "T. B. of Physiol.," vol. ii, p. 1157, 1900.

Taste is rarely referred to as being morbidly influenced by disorders of the pituitary, but it is probable that the condition of this sense is seldom inquired into. It is occasionally mentioned, however, among the symptoms of acromegaly and tumor. In Gibson's case, the food had to be highly seasoned before it could be tasted. In a case which proved to be one of melanotic sarcoma of the pituitary observed by Agostini[127] impairment of taste coincided with auditory, visual and olfactory paræsthesia and with "obtuse general sensibility." Here again we have not only glosso-pharyngeal fibers and the lingual terminals of the chorda tympani, but also the lingual branch of the 5th, which supplies the anterior two-thirds of the tongue with common sensibility.

This terminates the list of special senses. It has become apparent that the only special sense clearly related with the posterior pituitary is that of general sensibility.

Although this organ thus asserts itself as a terminus for impressions included within the precincts of a single special sense out of the five, the function it fulfills in this connection is a far-reaching one as interpreted from my standpoint, since it means "the sensations of one kind or another from the body at large," including those from the gastro-intestinal mucous membranes, the muscles, etc.

We can now understand why Mills could write that "innumerable cases have been reported of lesions of the cortex" or excision of portions thereof failed to produce "the slightest impairment of sensibility," and why Schäfer was unable to say whether cutaneous sensibility was localized at all in the cortex. The foregoing facts obviously show that the cortex is not the organ through which such sensations are perceived. Indeed, Cyon's observation in relation to the loss of sensibility of the nasal mucous membrane after removal of the pituitary is but a limited example of the morbid influence of this procedure: Vassale and

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[127] Agostini: Rivista di patol. Nerv. e Ment., Fasc. iv, 1899.

Sacchi[128] found that the animals submitted to it remained *totally indifferent to excitation*—evidence that their general sensibility had been destroyed. It is plain, therefore, that the posterior or neural lobe of the pituitary body receives impressions of general sensibility from the body at large.

Sensory impulses of this kind awaken normal *motor* stimuli in animals deprived of their brain. Thus in Goltz's dog, there was no loss of muscular co-ordination although the animal was not, of course, deprived of its pituitary. And yet, this phenomenon always attends removal of this organ, even though the cerebellum and the semicircular canals be normal. The pituitary body must, therefore, exercise an all-pervading influence over motor phenomena. What is the nature of this influence?

Clinical data throw considerable light upon this question provided several confusing facts are borne in mind and misleading cases are avoided. First among the former, is the reserve of functional elements with which the pituitary body, in common with the "ductless glands," is endowed, which makes it possible for this organ to carry on its functions even though considerable of its substance is destroyed. Thus, Vassale and Sacchi[129] in the course of their experiments on cats and dogs, in which total extirpation of the pituitary invariably proved fatal, only partially destroyed it in one of these animals, as previously stated. The characteristic phenomena were observed for about three weeks, after which the animal gradually recovered and remained healthy. At the end of eleven months it was killed and the incomplete destruction was confirmed. Friedmann and Maas[130] also refer to three animals which were killed after two and one-half, three and four months after a supposed destruction of the organ; but this was found to have been incomplete.

This partial destruction may be due to disease. As emphasized by Burr and Riesmann,[131] the pituitary body can also carry on its functions, even though a part of it be diseased. Thus in a case of tumor of this organ in which no signs of acromegaly were present, they found a considerable portion of its elements intact. In a case reported by Walton, Cheney and Mallory[132] a part of the pituitary body was also found normal.

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[128] Vassale and Sacchi: Rev. sper. di fren., p. 83, 1894.
[129] Vassale and Sacchi: *Ibid.*
[130] Friedmann and Maas: *Loc. cit.*
[131] Burr and Riesmann: Jour. of Nerv. and Mental Dis., Jan., 1899.

Another clinical feature which tends to obscure the rôle of the pituitary body is the extension of a morbid process in this organ to structures above, or the presence, simultaneously, of cerebral, bulbar or spinal lesions. The cases quoted herein are of such a nature as to prevent confusion on this score; they include only such disturbances as those witnessed experimentally either during stimulation or after extirpation in normal animals.

Irrespective of these sources of confusion, the functional relationship between the pituitary and the muscular system may easily be discerned. Thus, while Pironne[133] found experimentally in common with other observers, that "the results of removal" are "disturbances of mobility, great depression, rapid emaciation, cachexia and death," Rath[134] enumerates the symptoms of tumor of the organ in the order of their frequency as follows: headache, generally frontal and temporal; vomiting; vertigo; disturbances of motion, spastic and paretic; disturbances of speech; disorders of the pupil; paralysis of the ocular muscles; diabetes mellitus and insipidus. The ocular motor disturbances, "vomiting," "motion" and "speech," bring into play almost all the muscles of the organism governed by the cranial nerves, including the tenth (vagus) and fifth. In Agostini's case of sarcoma of the pituitary, muscular asthenia was a prominent symptom, although the characteristic signs of acromegaly were absent. In another case of tumor reported by Howard and Southard,[135] "some unsteadiness of gait" was noted four years before death, suggesting not only muscular weakness but impairment of co-ordination. In Walton, Cheney and Mallory's case,[136] an angiosarcoma had destroyed the pituitary in part, without giving rise to clearly-defined symptoms of acromegaly; and yet the patient's gait was "slow and dragging" and the muscular weakness increased until "extreme prostration" was reached. In a case characterized as "ataxia but without any signs of acromegaly," observed by T. W. P. and J. Lawrence,[137] the pituitary was found enlarged and the posterior lobe was destroyed. Masay[138] observed that after removal of the pituitary body, the animals (dogs) though they tried to do so, were "unable to stand," the ataxia being "complete."

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[132] Walton, Cheney and Mallory: Boston Med. and Surg. Jour., Dec. 7, 1899.
[133] Pirrone: La riforma medica, Feb. 25, p. 205, 1903.
[134] Rath: Archiv f. Ophthal., Bd. xxxiv, Hft. 4, S. 81, 1888.
[135] Howard and Southard: Amer. Jour. Med. Sci., Oct., 1904.
[136] Walton, Cheney and Mallory: *Loc. cit.*
[137] T. W. P. and J. Lawrence: Brit. Med. Jour. Apr. 8, 1899.

Such paralytic phenomena also occur in advanced acromegaly. Here, muscular asthenia is a prominent feature. Even in cases such as those reported by Virchow, Dana, Woods Hutchinson and others in which there is marked increase in bulk and muscular strength, in wrestlers, giants, etc., this symptom forms part of the cachectic stage into which the patient ultimately lapses. "In the earlier stages in *some* cases," writes Woods Hutchinson,[139] "there is a decided increase in both muscular bulk and power, but this rapidly reaches a maximum and thereafter quickly declines." But he also concludes in accord with Dana, Tamburini and Harlow Brooks, that acromegaly and giantism are "the result of a normal or glandular hypertrophy of the entire pituitary body beginning in and chiefly affecting the anterior lobe, but even extending to and affecting the posterior or nervous lobe." All cases of acromegaly which do not die of some intercurrent disease, in fact, lapse into what amounts practically to muscular impotence.

And we have here but the uncomplicated type. Along with the muscular asthenia we may have mixed symptoms. Where in other words there was merely "increasing weakness," with "no evidence of paralysis" we now witness besides, phenomena recalling neuroses and muscular dystrophies of various kinds—syringomyelia; unilateral, bilateral or localized paralyses; progressive muscular atrophy, etc. In some cases related by Duchesnau[140] for instance, "atrophy of the muscles was so marked, that it had been mistaken for syringomyelia, progressive muscular atrophy" and other kindred disorders. In a case reported by Pirie[141] (who quotes Duchesnau's), the muscular weakness not only became intense, but this was attended by atrophy of various muscles of the hands, arms, calf, thigh, and of the glutei.

On the whole, it is evident that the "neural" or posterior lobe of the pituitary, when diseased alone or in conjunction with the anterior lobe, can provoke a great variety of motor disorders, a fact which, in view of the loss of muscular co-ordination, the marked relaxation of all muscles and the profound asthenia that follow extirpation of the pituitary—including of course the neural lobe—clearly point to the latter as the seat of general motor centers. Its influence is not limited to the skeletal muscles, since, as we have seen, it governs also the sympathetic system, whose terminals are distributed to the muscular coat of the arterioles.

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[138] Masay: *Loc. cit.*, pp. 16, 17.

[139] Woods Hutchinson: N. Y. Med .Jour., Mar. 12, Apr. 2, 1898; July 21 and 28, 1900.

[140] Duchesnau: Thèse de Lyon, 1891.

[141] Pirie: Lancet, Oct. 5, 1901.

We can now understand why organic lesions, gradually as they destroy the cellular elements of the posterior pituitary, give rise to promiscuously-distributed disturbances of sensibility and motility. It receives sensory impulses from all muscles, skeletal, gastric, intestinal, diaphraghmatic, cutaneous, ocular, etc., and from the mucous membranes, then converts and co-ordinates all these impulses into motor stimuli which it sends back to the muscles, to sustain the many functions with which they are connected and to enhance their activity, when need be.

The view still prevails in the minds of many that the cerebellum is the co-ordinating center of muscular movements. Foster says, in this connection, that experimental and clinical investigations "have thrown little or no light on the exact nature of the part which the organ plays in the complex process, but perhaps rather show that *we are at present wholly ignorant of how co-ordination is brought about.*" He states also, however, referring to the pituitary body: "Concerning the purposes of the organ as a whole, we know absolutely nothing." The foregoing evidence, contributed since he wrote these lines, clearly suggests that the true co-ordinating center is the neural lobe of the pituitary body.

Foster[142] terms "the machinery of co-ordinated movements" structures "lying between the cerebral hemisphere above and the top of the spinal cord below;" but as to *how* "this machinery is related to the various elements which go to make up this part of the brain" he says "the only answers which we receive are of the most imperfect kind." Physiologists, in fact, have furnished no answer. Experimental evidence, however, has brought them to structures *immediately overlying the pituitary body*

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[142] Foster: *Loc. cit.*, p. 951.

and connected with it, but structures presenting no organization capable, after removal of the brain, of accounting for the continuation of all somatic functions. We have seen that Ramon y Cajal—though unaware of the functional importance of the pituitary body—found that it was connected by afferent and efferent, *i.e., sensory* and *motor* fibers with the great nucleus situated immediately above this organ, which nucleus, as previously shown, is itself connected by nerve-paths with "the top of the spinal cord below." The neural lobe of the pituitary thus asserts itself as the chief center of the "machinery of co-ordinated movements," as well as the seat of common sensibility.

The vast scope of these functions is summarized in the following postulates: (1) *the cortex is not the only organ through which cutaneous and internal sensations are directly perceived;* (2) *these sensations, which include pain, heat, cold, pressure (constituting touch), hunger, thirst and the muscle and spatial senses, are perceived by and through the neural or posterior lobe of the pituitary body;* (3) *this organ also receives all sensory impulses which reflexly incite and sustain the secretory activity of all glands (gastric, intestinal, pancreatic, salivary, lachrymal, lacteal, etc.), and the contraction of all muscles, striped and unstriped, peripheral or internal (including those of the vessels and heart, the stomach, intestines, bladder, etc.)*; (4) *the processes thus governed by the posterior pituitary body, are not mere reflex phenomena such as those elicited from subsidiary nerve-centers, e.g., those in the medulla oblongata and spinal cord; they include all functions which require conscious and to a certain extent intelligent co-ordination.*

This involves the conclusion that *the neural lobe of the pituitary is the general center of all the cranial nerves concerned with common sensation and motion,* besides the sympathetic center studied in the preceding section, with which the cranial centers are in close functional association, as will be shown.

The manner in which these nerves carry on their functions in the peripheral organs, and their functional relations with the sympathetic terminals will be studied in the eighteenth and twentieth chapters.

THE PITUITARY BODY AS THE GOVERNING CENTER OF THE ADRENALS, AND AS THE THERMOGENIC AND RESPIRATORY CENTER.

In the first volume, I pointed out that the pituitary body contained the adrenal center. The importance of this conclusion is apparent in view of the fact that the adrenals are the source of the secretion which, in the lungs, becomes adrenoxidase. This is further emphasized by the relationship of the pituitary body, as heat center, with the function of oxygenation. We saw in the preceding section, that the supposed heat "centers" found by Ott and others in the floor of the third ventricle were in reality not centers, and that the effects produced were due to irritation of the nerve-paths from the pituitary body which reached the spinal cord by way of the basal tissues.

In the preceding section, it was shown also that the sensory and motor nerves to and from the pituitary body were connected with the mass of gray matter overlying the infundibular opening in the floor of the third ventricle, the giant-celled supra-infundibular nucleus, and that the sympathetic nerve-paths took this route. A suggestive feature asserts itself in this connection: While these motor paths (which, as shown by the researches of comparative anatomists, especially Edinger, are probably present in all vertebrates) correspond clearly with those observed histologically by Ramon y Cajal, the fibers which Gentès traced from the neural or posterior lobe of the pituitary to the tuber cinereum in the floor of the third ventricle, and which Andriezen traced directly from the pituitary to the neighborhood of the pons, were not involved in these functions, and have remained, as it were, without occupation. Now, the fibers traced by Gentès are precisely those derived indirectly from the sensitive cells (similar to those of the olfactory area) which this investigator found in the partition between the two lobes of the pituitary, and which area I assimilate to the test-organ of mollusks, the lower chordata, etc.

That the fibers from the test-organ form part of the nerve-chain which terminates in the adrenals, is suggested also by the fact that it is also among its fibers in the tuber cinereum that punctures—from below by way of the mouth as well as from above—were found by Ott, and others after him, to cause a marked rise of temperature. With the adrenals as the source of the secretion which, converted into adrenoxidase, supplies the entire organism with oxygen, and a direct nerve-path from the "test-organ" of the pituitary, by way of the floor of the third ventricle and the cord, to the adrenals, we have a self-evident mechanism to explain an obscure function, *i.e.*, the manner in which the temperature is raised.

Another important function is linked intimately with this mechanism, viz., that of *respiratory* center. Soury,[143] quoting Ott, states that "the gray substance of the anterior portion of the floor of the third ventricle" (immediately above the pituitary body) is "identical with the thermo-polypnœic center" and that "removal of this center diminishes the number of respiratory movements." Ott therefore regards the tuber cinereum as a "center of polypnœa and *thermo*taxis." In view of the foregoing facts, this points not only to the "test-organs" as the thermogenic or "heat" center, but also as the *polypnœic* or *respiratory* center, and, moreover, to the tuber cinereum as the bed for the nerve-paths from these centers to the pons and medulla. This adds testimony as to the functional connection between the pituitary body and the adrenals, since it is the secretion of the latter which, as adrenoxidase, supplies oxygen to the entire organism.

The rôle of the respiratory center involves, however, a concomitant influence upon the large array of inspiratory and expiratory muscles (chest, diaphragm, abdomen, etc.) which carry on their functions rhythmically without voluntary control. We have seen in the preceding section that the posterior lobe of the pituitary, in which the thermogenic fibers arise, is also the origin of the nerve-chains that govern muscular activity. In most text-books the respiratory center is said to be located in the medulla near the vasomotor center. As Howell[144] says, however, "the region has been delimited by vivisection experiments only" and "no especial group of cells can be found in this region sufficiently separated anatomically to make it probable that they constitute the center in question." This cannot be said of the posterior pituitary body. Not only does it present all the attributes of a highly differentiated co-ordinating organ, such as the presence of various centers closely connected functionally requires, but its removal (with the anterior lobe) is followed, as we have seen, by marked muscular relaxation, dyspnœa and hypothermia.

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[143] Soury: *Loc. cit.*, vol. ii, p. 1256.
[144] Howell: "T. B. of Physiol., p. 611, 1905.

The adrenals thus represent the normal terminal of a nerve-chain which begins in the "test-organ," passes thence by way of the neural lobe of the pituitary to the tuber cinereum and then to the ponto-medullar region. Here, a continuation of this path is evidently present, for Reichert[145] refers to a "pontobulbar *thermo*augmentor center," the presence of which in this location he determined experimentally. What is the course of the adrenal nerve-path from this region to the adrenals?

Goltz and Ewald[146] have shown that an animal from which the entire spinal cord below the bulb had been removed—thus leaving intact all the cranial nerves and the basal structures, including the pituitary body—could live several years. Soon after the operation the vessels recover their tonicity and the circulation becomes practically normal. Yet there occurs a curious phenomenon which continues several weeks: the animal is in constant danger of death from *cold* unless it be kept in a superheated medium. Goltz emphasized another striking feature, *i.e.*, the occurrence of marked trophic bilateral lesions of the skin when, in gradually shortening the cord from below, in successive operations, he reached the upper *dorsal* vertebra. These two features suggest that the upper part of the cord is of great functional importance in thermogenesis and nutrition. Claude Bernard[147] had shown many years before that transection of the cord in the upper dorsal region could bring the rectal temperature down 16° C. (28.8° F.) in five hours. Indeed, Pochoy[148] found that a section in this region brought the rectal temperature down over 22° C. (41.6° F.) in twenty-four hours in guinea-pigs and that it continued to decline until death ensued. It is evident, therefore, that division of the upper dorsal cord seriously invalidates the thermogenic apparatus.

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[145] Reichert: Jour. Amer. Med. Assoc., Jan. 18, 1902.
[146] Goltz and Ewald: Archiv f. d. ges. Physiol., Bd. lxiii, pp. 362, 400, 1896.
[147] Claude Bernard: "Leçons sur la chaleur animale," p. 161, 1876.
[148] Pochoy: Thèse de Paris, 1870.

The truth of this is emphasized by the fact that transection of the cord lower down causes only temporary torpor of the automatic functions. "If we wait for a time," says Stewart,[149] "we shall find that this torpor of the *lower dorsal* and lumbar cord is far from giving a true picture of its normal state; that, cut off as it is from the influence of the brain, it is still endowed with marvelous powers. If we wait long enough, we shall see that, although voluntary motion never returns, reflex movements of the hind-limbs, complex and co-ordinated to a high degree, are readily induced. Vasomotor tone comes back. The functions of defecation and micturition are normally performed." As I will show below, this is due to the fact that the nerves to the adrenals are not included in the portion of the cord separated from the centers. The subsidiary vasomotor centers in the lower or separated segment of the cord being nourished and oxygenized as usual after the shock of the operation has passed and when a collateral circulation is reëstablished, the vasomotor functions are resumed. This explains also why the process of repair proceeds unfailingly, whereas section in the upper portion of the cord, unless great precautions are taken, follows a lethal course.

Ott[150] states that "destruction of the spinal cord from the *fifth dorsal* vertebra down permits the animal to generate *as much heat as before* the operation." This harmonizes with my own conception of the process: below this level, the only morbid phenomenon connected with the circulation which can be caused is vasodilatation; hence the comparatively benign results. Above it, however, the transection involves not only the vasomotor supply, but, also, the "thermogenic" nerves, *i.e.*, those to the adrenals. It follows that these nerves constitute an autonomous path, one totally independent of the vasomotor path. Now this has repeatedly misled physiologists. Overlooking the presence of this independent thermogenic nerve, they have ascribed to vasomotor influence, vasoconstrictor phenomena that were due to stimulation of the adrenals, the secretion of which, as is well known, causes a rise of the blood-pressure. "Hardly any other agent will produce such an enormous increase of pressure," writes Schäfer,[151] referring to injections of adrenal extract after division of the vagi, "except direct stimulation of the vasomotor center."

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[149] Stewart: *Loc. cit.*, p. 694.
[150] Ott: *Loc. cit.*, p. 248.

Moreover a *dual effect* is produced when this part of the path or its branches are stimulated which does not occur when the influence of the adrenals is removed. Thus, François-Franck and Hallion[152] have shown that the vasomotor nerves of the liver leave the spinal cord by the rami *below* the fifth, *i.e.*, the sixth down to the second lumbar. These limits have been confirmed by Langley.[153] The former physiologists remark, however, that "centrifugal excitation of the *vertebral* nerve (composed of four or five of the lower cervical nerves) after section of the upper rami communicantes (from the *first* to the *fifth*) *no longer* produces hepatic vasoconstriction"—a statement which implies that stimulation of the vertebral nerve *does* produce hepatic vasoconstriction. The manner in which this effect is brought about, François-Franck and Hallion were unable to explain, however; they ascribed them therefore, to "reflex action" or to some *unexplained "indirect influence."* This influence, interpreted from my standpoint, is that of the adrenals.

The mode of action of the adrenal secretion, in the light of the facts submitted in the first chapter, is, of course, indirect, in the sense that it is first of all converted into adrenoxidase. This latter substance being the activating agent in all metabolic processes, an excess in the blood enhances its oxygenizing power in proportion. When such blood is supplied to the arteries and veins by their vasa vasorum, their muscular elements are abnormally stimulated and contract, reducing the caliber of the vessels.

The thermogenic fibers proceeding no further down the cord, as shown by Ott's experiment, than the fifth dorsal vertebra, this "unexplained indirect influence," *i.e.*, overactivity of the adrenals, should occur when the upper five dorsal nerves (which pass to the sympathetic cord of ganglia) are stimulated.

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[151] Schäfer: "T. B. of Physiol.," vol. I, p. 955, 1898.
[152] François-Franck and Hallion: Arch. de physiol., T. viii, No. 5, p. 936, 1896.
[153] Langley: Schäfer's "T. B. of Physiol.," vol. II, p. 644, 1900.

François-Franck and Hallion found that stimulation of the sympathetic chain where, they state, "*it has not as yet received from the spinal cord the hepatic vasoconstrictor rami*" caused "a marked rise of aortic pressure." Even more striking is the effect produced when the sympathetic cord had been *isolated* by dividing the rami containing the *hepatic vasomotor nerves*. This caused, as stated by these physiologists and as shown by their tracings, "the *maximum vasomotor effect*." Obviously, the upper portion of the sympathetic chain was capable of causing, irrespective of any vasomotor influence, a very marked increase of vascular tension in the liver—an effect due to the general rise of blood-pressure caused by the excessive adrenal secretion, *i.e.*, adrenoxidase, produced.

What is the identity of the nerves which, out of the five upper dorsal nerves, produce this effect by transmitting centric impulses to the adrenals?

These impulses doubtless pass to the sympathetic chain through more than one ramus. Thus, François-Franck and Hallion state: "Division of the upper root was followed by marked reduction of the vasoconstrictor effect," but they do not refer to the specific influence of the four remaining rami. Fortunately, however, this gap is filled by the experiments of Biedl to which reference was made in a previous chapter.[184]

We have seen that it was on stimulating the peripheral end of the cut splanchnic that he increased the secretory activity of the adrenals, a result confirmed by Dreyer. Biedl thus showed that the splanchnic contained the secretory nerves of the adrenals. In order to ascertain, if possible, whether these organs contained vasomotor nerves also, he exposed and divided all the spinal roots from the *third* thoracic to the third lumbar, and stimulated both their anterior and posterior segments "with a strong induction current." Not only did he not observe vasoconstrictor effects, in the adrenals, but he failed to obtain any evidence of overactivity of these organs, *i.e.*, an increased blood-flow through them. This experiment—which Biedl repeated three times, always with the same result—indicates that the secretory nerves to the adrenals do not originate in the spinal cord up to the third thoracic.

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[184] *Cf.* this vol., p. 819.

This gives us the identity of the path to the adrenals. Inasmuch as François-Franck and Hallion markedly reduced the "maximum vasomotor effects" (so-called) observed by them, by dividing the first thoracic ramus, a part of these effects remains unaccounted for. This is supplied by Biedl's experiment since it left, as the only ramus to supply this want, the second. This points to the *first* and *second dorsal rami* as the paths of the thermogenic fibers to the sympathetic chain and thence to the greater splanchnic.

Additional experiments suggest, however, that the third thoracic ramus likewise contains fibers to the adrenals and that Biedl did not detect them because impulses through a single bundle were inadequate to satisfy the needs of a process carried on normally through three sets. Thus precisely as François-Franck and Hallion obtained hepatic (so-called) "vasomotor" effects by stimulating the sympathetic chain *above* the course of the liver's true vasomotor nerves, so have Bulgak, Schäfer and Moore and Bunch obtained "vasomotor" effects in various organs from the third thoracic nerve, among others, though their normal vasomotor paths are lower down. Bunch,[155] for example, had established the limits of the innervation of the small intestine from the sixth thoracic and fifth lumbar, inclusive. Later, however,[156] he likewise obtained "vasomotor" effects in the small intestine by stimulating the upper thoracic nerves from the second down. Langley,[157] referring to these results, expresses his belief that the origin of these nerves is less extensive and that the uppermost nerve to send fibers to the solar ganglia is the *fourth* or fifth thoracic. Yet, we cannot doubt that the above-named physiologists, including Bunch, obtained "vasomotor" effects by stimulating nerves above the fourth thoracic: but only through the intermediary of the adrenals.

Indeed, a nerve-path is present in the sympathetic chain which is *distinct* from the true vasomotor, and which extends to the upper thoracic limit of the sympathetic chain. Quain,[158] for instance, states that some fibers of the splanchnic's higher roots "may be traced upward in the sympathetic cord as far as the *first* and *second* thoracic ganglia. Gray[159] gives the same limits. Cruveilhier[160] says that these filaments "are merely *in contact* with the sympathetic."

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[155] Bunch: Jour. of Physiol., vol. xxii, p. 357, 1898.
[156] Bunch: *Ibid.*, vol. xxiv, p. 72, 1899.
[157] Langley: Schäfer's "T. B. of Physiol.," vol. ii, pp. 644 and 695, 1900.
[158] Quain: "Anatomy," seventh edition, vol. ii, 1867.

Proof that the adrenal secretion can produce vasomotor effects may also be furnished by showing that in the parts influenced, the small intestine, for instance, there are, as in the case of the liver, two distinct forms of vasoconstriction, one due to vasomotor nerves and the other to the local action of adrenoxidase, and that when one is removed the other persists. Intestinal inhibition affords evidence of this dual action. We have seen that "inhibition" is merely excessive vasoconstriction. Now, Schiff, Ludwig and Kupffer, Bechterew and Mislawsky (Starling[161]) have observed both a motor effect (increased peristalis) sometimes, and inhibition at others. Bunch has also shown that stimulation of the splanchnic could cause increased intestinal activity and at other times inhibition. "Jacobi," says Starling, in a review of the subject, "states that the intestinal inhibitory fibers of the splanchnics take a different course from the vasomotor fibers, and that section of the nerves running from the *suprarenals* to the solar plexus *annuls* the inhibitory action of the splanchnics *without affecting their vasoconstrictor effect.*" Suppression of the adrenal influence in this experiment obviously prevented excessive vasoconstriction.

It is evident, therefore, that the *first, second* and *third* thoracic nerves—the three *above* the uppermost limit set by Langley for sympathetic vasomotor fibers which run to the solar plexus—constitute a separate path, the secretory nerves to the adrenals.

Having attributed to the pituitary the rôle of "heat" center, owing to a nervous connection with the adrenals, and the presence of such a connection having now been shown to exist, the adrenal secretion should be capable of raising the temperature when in excess (as adrenoxidase) in the blood. This is a recognized effect of adrenal extractives. Thus Oliver and Schäfer[162] observed under its effects "slight *transitory* disturbance of the rate of the heart beats, of the respiration, and of the body temperature." Pellacani,[163] Foà[164] and other physiologists have likewise observed, besides the characteristic effects, a rise of temperature. E. T. Reichert[165] noted that among other effects an intravenous injection of 0.0005 gramme adrenalin caused "an increase of general metabolism and body temperature." His experiments showed that "the pulse and arterial pressure are the first to be affected, then the respiratory movements, and then general metabolism and body temperature." This is a suggestive sequence when we consider that the adrenal secretion, after absorbing oxygen in the lungs, becomes, as I have shown, the body's oxygenizing principle. Conversely, we have seen that removal of the adrenals, precisely as is the case when the pituitary body is destroyed, is followed by a steady decline of the temperature until death occurs.

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[159] Gray: "Anatomy," fifteenth edition, 1901.
[160] Cruveilhier: "Anatomy," Amer. edition, 1844.
[161] Starling: Schäfer's "T. B. of Physiol.," vol. ii, p. 312, 1900
[162] Oliver and Schäfer: Jour. of Physiol., vol. xviii, p. 230, 1895.

Finally, blocking of the vessels which carry the adrenal secretion to the inferior vena cava not only causes a marked decline of the blood-pressure by decreasing the activity of the metabolic exchanges in the vascular walls, but it arrests also all oxidation processes, *i.e.*, life itself. Thus Strehl and Weiss[166] found that after removing one adrenal, the blood-pressure could be lowered by clamping the suprarenal vein of the remaining organ, thus depriving the blood of any adrenal secretion, and that by releasing this vein the blood-pressure was soon restored to its previous level. When the second adrenal was also removed, the blood-pressure at once fell 20 to 30 mm. Hg., and continued to fall slowly until death ensued.

This explains why Gray,[167] alluding to the suprarenal plexus, remarks: "The branches of this plexus are remarkable for their large size in comparison with the size of the organ they supply." The function they govern through the adrenals, as I have now shown, is one of the most important of the organism.

That there exists a functional relationship between the pituitary and the adrenals is shown also by the pathology and symptomatology of various disorders in which the pituitary is either implicated or the seat of primary lesions.

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[163] Pellacani: Archiv per le scienze med., vol. iii, No. 24, 1879..
[164] Foà: *Ibid.*, vol. iv, p. 451, 1880.
[165] E. T. Reichert: Univ. of Penna. Med. Bull., Apr., 1901.
[166] Strehl and Weiss: Pflüger's Archiv, Bd. lxxxvi, S. 107, 1901.
[167] Gray: "Anatomy," fifteenth edition, p. 808, 1901.

In *Addison's disease*, the lesions are usually situated in the adrenals or in the nervous connections of these organs; and yet the phenomena witnessed are the counterpart, so to say, of those that attend destructive disorders of the pituitary. Thus Schäfer[168] states that the symptoms that follow removal of the pituitary body are "(1) diminution of the body temperature; (2) anorexia and lassitude; (3) muscular twitchings and tremors, developing later into spasms; (4) dyspnœa"—the list, we have seen, of phenomena that follow removal of the adrenals. Again, Harlow Brooks,[169] referring to the cachectic stage of acromegaly, states that "a general brownish pigmentation is present in the average case which at times strongly resembles that found in Addison's disease." E. Wasdin,[170] in a case of fracture of the maxillary and sphenoid implicating destruction and gangrene of the pituitary body, verified after death, observed among other symptoms, bronzing of the skin.

The extreme muscular weakness following removal of the pituitary to which Schäfer refers was also witnessed, as we have seen, by many other physiologists, the "ataxia being complete" in Masay's dogs. A similar condition follows the removal of the adrenals. Thus, Brown-Séquard called attention to the "progressive paralysis" which followed this procedure. Abelous and Langlois[171] observed the same effects in frogs, the paralysis beginning in the lower limbs and spreading anteriorly. Boinet[172] noted the same symptom in fifty-nine rats: the movements became slow, then impossible. Several other investigators have also referred to this symptom.

Tracing the pathological changes found in this disease outside of the adrenals, the semilunar ganglia are the first to appear. These structures, as is well known, are often found congested, caseous, sclerosed, etc. Now, removal of these ganglia, as stated by Rolleston,[173] is followed by "rapid emaciation, asthenia, low temperature, diminution of the amount of urea in the urine." These are all subjective symptoms of Addison's disease; while the reduced urea output points to reduced metabolism, *i.e.*, lowered oxygenation. The path thence to the cord, the splanchnic nerves, may be found to contain degenerated fibers. Jürgens[174] even goes so far as to state that gray degeneration is always present in the splanchnic in true cases of Addison's disease. What he found was doubtless broken-down chromaffin cells, first described by Henle in 1865, as constituents of the adrenals, but which subsequent observers found also in the ganglia adjoining the adrenals in birds (Rabl),[175] in the splanchnic nerves of amphibia and reptiles (Zellnester),[176] in the ganglia of the sympathetic chain (Kose),[177] and which, as shown recently by Wiesel,[178] are destroyed in Addison's disease. Tizzoni,[179] Kalendero and Babès,[180] and many others have found spinal lesions, a fact confirmed experimentally by Alezais and Arnaud,[181] who found ascending degeneration of the lateral columns of the cord in animals that had survived sufficiently long removal of the adrenals. Even the pituitary body may show lesions. Thus Pansini and Benenati,[182] in a typical case of Addison's disease in which the whole cutaneous surface was a deep bronze color, found both adrenals in a state of caseous degeneration and the pituitary body markedly enlarged. This hypertrophy, verified microscopically, is readily accounted for when the organ is considered as the governing center of the adrenals: it was the result of overactivity, having for its purpose to enhance the secretory activity of what remained of the diseased adrenals, in order to sustain as long as possible the oxidation processes of the organism at large.

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[168] Schäfer: *Loc. cit.*, vol. i, p. 946.
[169] Harlow Brooks: Archives of Neurol. and Psychol., vol. i, p. 485, 1898.
[170] E. Wasdin: Monthly Cyclop. of Pract. Med., Mar., 1903.
[171] Abelous and Langlois: Archives de physiol. norm. et path., 5 Série, vol. iv, p. 269, 1892.
[172] Boinet: Marseille méd., Sept. 1, 1899.
[173] Rolleston: Allbutt's "Practice of Medicine," vol. v, p. 540, 1897.

Briefly, removal of the pituitary body not only produces symptoms similar to those that attend Addison's disease or follow removal of the adrenals, but when ascending degeneration occurs in Addison's disease, it proceeds along the nerve-paths that unite the adrenals to the pituitary body.

Acromegaly is another disease which emphasizes the functional relationship between the pituitary body and the adrenals. It is especially interesting in this connection because its initial lesion occurs in the anterior lobe, that to which the test-organ (though forming part of the partition) really belongs. Thus, while Massolongo[183] ascribed acromegaly to hyperactivity of this organ, Tamburini[184] identified as cases of true acromegaly only those characterized by hypertrophy and over-activity of the anterior lobe. This was confirmed by Harlow Brooks[185] in a study limited to cases in which the pituitary had been examined microscopically, who found in every instance reported, save one, that the enlargement of the organ had been confined to the anterior lobe.

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[174] Jürgens: Deut. med. Woch., Bd. xi, S. 153, 1885; Berl. klin. Woch., Bd. xxi, S. 824, 1884.

[175] Rabl: Archiv f. mikrosk. Anat., Bd. xxxviii, S. 492, 1891.

[176] Zellnester: Sitzungsb. d. Kais. Akad. v. Wien, Bd. lxvi, Abth. i, S. 121, 1872.

[177] Kose: Anat. Anzeiger, Bd. xxii, S. 162, 1902.

[178] Wiesel: Zeit. f. Heilkunde, Bd. xxiv, S. 257, 1903.

[179] Tizzoni: Mem. della R. Acc. dell Scienze, Bologna, ser iv, T. ix, p. 27; London Med. Recorder, Feb. 20, 1890.

[180] Kalendero and Babès: La Semaine médicale, Feb. 22, 1899.

[181] Alezais and Arnaud: Revue de méd., vol. ii, p. 283, 1891.

[182] Pansini and Benenati: Il Policlinico, Apr. and May, 1902.

With the test-organ of this lobe directly connected by nerve-paths with the adrenals, and the latter as the source of the secretion which becomes adrenoxidase and sustains tissue metabolism, and therefore nutrition, we have a normal explanation of the underlying cause of the disease, *i.e.*, hypernutrition. This feature—though unexplained so far—has in fact formed the basis of most theories as to the pathogenesis of the disease. Dallemagne,[186] for instance, ascribes it to the presence of trophic centers in various parts of the nervous system. Von Recklinghausen[187] considered acromegaly as a trophic neurosis dependent upon auto-intoxication. Mossé looked upon the disease as a trophic neurosis of vasomotor origin. Klebs[188] ascribed it to over-development of the vascular system combined with thymic hyperactivity, etc. The effects of overnutrition are shown with especial clearness in the acromegalic giants, in which the overgrowth is widespread instead of being restricted to the bones.

The familiar vascular lesions of the disease also indicate that overactivity of the adrenals—due to morbid stimulation by the test-organ—is a prominent feature of the disease. In a case reported by Harlow Brooks,[190] the posterior pituitary was found normal on microscopical examination. Its connection with the infundibulum was normal, "though the remainder of the pituitary body," says the author, was "made of the enlarged anterior lobe." It proved to be a case in which the test organ lobe was alone diseased. Now, the vascular lesions were also typical of acromegaly. Examined histologically, the small arteries showed hyperplasia, proliferation of the endothelial cells of the intima, etc.,—all signs of active engorgement—and the large ones fibrous thickening. With overactivity of the test-organ as the source of correspondingly energetic stimuli to the adrenals, this morbid process is clearly explained: an excessive amount of adrenal secretion, *i.e.*, adrenoxidase, is continuously present in the blood, and the vascular walls, receiving such blood through their vasa vasorum, are the seat of hyperplasia, proliferation, etc. In the larger vessels this morbid process, owing to the greater blood-supply, is pushed beyond this stage, *i.e.*, to that of fibrosis. The enlargement of the extremities, bones and soft tissues, including the proliferation of capillaries, and the hypertrophy of the muscles during the erethic stage, are normal sequences of such a process, the capillary system being not only constantly gorged with blood, owing to the state of contraction to which both the arteries and veins are submitted, but with blood whose oxygenizing properties exceed the normal. The general symptoms of Brooks's case plainly indicate excessive peripheral hyperæmia, viz., hyperæsthesia, "hot-flesh," as expressed by the patient, polyuria, etc. Glycosuria was likewise present, a symptom clearly traceable, as shown below, to overactivity of the adrenal center—the test-organ of the anterior pituitary.

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[183] Massolongo: Riforma Med., vol. viii, p. 10, 1892, and Centralbl. f. Nervenh., Bd. xviii, S. 281, 1895.

[184] Tamburini: Rivista sper. di fren., p. 559, 1894, and 414, 1896.

[185] Harlow Brooks: *Loc. cit.*

[186] Dallemagne: Arch. de méd. exp., T. vii, p. 589, 1895.

[187] Von Recklinghausen: Arch. f. path. Anat., Bd. cxix, S. 36, 1890.

[188] Mossé: Mercredi médical, Sept. 11, 1895.

[189] Klebs: "Allgemeine Pathologie," Bd. ii, 1889.

[190] Harlow Brooks: *Loc. cit.*

Dystrophia adiposogenitalis.—It has been generally believed that this disease, particularly since the experimental and surgical observation of Biedl,[1900a] Paulesco,[1900b] and Cushing,[1900c] that this disease was caused by lesions of the anterior lobe, but Cushing and Fisher,[1900d] have also attributed it to lesions of the posterior lobe. Blair Bell,[1900e] referring to these authors, states that the only way in which he was able to produce the disease experimentally was by separating or clamping the stalk which connects

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[1900a] Biedl: Innere Sekretion, second edition, 1913.
[1900b] Paulesco: L'hypophyse du Cerveau, Paris, 1908.
[1900c] Cushing: The Pituitary Body and its Disorders, 1912.
[1900d] Fisher: Hypophysis, Akromegalie und Fettsucht, Wiesbaden, 1910.
[1900e] Bell: The Pituitary, New York, p. 244, 1919.

the pituitary with the base of the brain, the infundibulum. Now, we have seen that all nerves passed upward from the neural or posterior lobe. Destruction or clamping of these nerves by arresting its impulses to the thyroid and adrenals, in particular, produced insufficiency of these organs, from my viewpoint, and the characteristic symptoms of these combined disorders.

Glycosuria, we have just seen, was present in Brooks's case, in which the anterior lobe, the seat of the test-organ, was alone diseased. M. Loeb[191] pointed out in 1884 that glycosuria was a frequent accompaniment of tumors of the pituitary body. A more recent study of the literature of acromegaly led him to conclude that the association of this disease with glycosuria could not be accidental. He found, moreover, that glycosuria did not occur during the post-operative life of animals from which the pituitary body had been removed, a fact which indicates that it is due to over-activity of the organ and not to insufficiency. Marie observed it in one-half of the cases he examined. Guy Hinsdale[192] states that the urine often contains sugar and refers to fourteen authors who had observed the symptom. In sixteen cases of diabetic acromegaly the records of which were studied by Launois and Roy[193] a tumor of the pituitary was always found. In every instance the presence of the pituitary neoplasm had been confirmed post-mortem. Schlesinger[194] also emphasized the frequent coincidence of acromegaly and diabetes, having observed the latter in three consecutive cases of his own.

As a result of these observations, investigators have been driven to the conclusion that a "diabetic center" must exist in the neighborhood of the pituitary. "The theory of Loeb," write Launois and Roy,[195] in this connection, that of "compression by the pituitary tumor upon adjoining parts, seems in accord with clinical observations (Finzi, Strumpell), and with an experimental fact recorded by Caselli.[196] A glycogenic center is supposed to exist, apparently in the region of the *tuber cin-*

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[191] M. Loeb: Centralbl. f. inn. Med., Sept. 3, 1898.
[192] Guy Hinsdale: "Acromegaly." Detroit, 1898.
[193] Launois and Roy: C. r. de la Soc. de biol., vol. lv, p. 382, 1903.
[194] Schlesinger: Wiener klin. Rundschau, Apr. 15, 1900.
[195] Launois and Roy: *Loc. cit.*
[196] Caselli: *Loc. cit.*

ereum, which is abundantly supplied with highly organized nervous elements (Caselli)." The cause of the glycosuria is self-evident in view of the fact that the path from the test-organ to the adrenals lies in the tuber cinereum: Caselli's experimental excitation of this structure, therefore, provoked glycosuria because it stimulated the adrenals.

A similar procedure in the course of the pituitero-adrenal path in the medulla likewise causes glycosuria. Claude Bernard's puncture is a familiar proof of the fact. "Bernard," says Schäfer,[197] discovered "that certain lesions of the central nervous system, and especially a puncture in the region of the floor of the fourth ventricle, which corresponds, as we now know, *very nearly* to the position of the vasomotor center, produces a condition of glycosuria." The glycogenic impulses evidently pass downward, for as shown by Chauveau and Kaufmann,[198] division of the spinal cord in the cervical and upper dorsal regions prevents the diabetes caused by removal of the pancreas. The same procedure had already been found by Bernard to cause hypoglycæmia. These are all normal results in view of the fact that, as I pointed out in the preceding chapter, the nerves to the adrenals pass down the cord, leave the latter in the three upper dorsal nerves to enter the sympathetic chain, and then the splanchnic. (See Frontispiece, Vol. I.) Such being the case, however, division of the splanchnic should likewise arrest glycosuria. Landois[199] says in this connection: "It is a remarkable fact that glycosuria, when present, can be removed by division of the splanchnic nerves." Even the glycosuria caused by Claude Bernard's puncture can be arrested by this procedure, an observation confirmed by Eckhard, Kaufmann[200] and others.

Finally, as is now well known, the adrenal extract, as shown by Blum,[201] Croftan,[202] Metzger,[203] Herter,[204] and others, causes glycosuria when injected subcutaneously, endovenously, or into the peritoneal cavity. Herter[205] found also that intravenous injections of adrenalin were followed by a large excretion of sugar and that "a rise of blood-pressure is an accompaniment of glycosuria"—the former phenomenon being, as is well known, a characteristic effect of adrenal extract. The adrenal secretion proper is doubtless able to produce a similar effect, for Herter and Wakeman[206] ascertained experimentally that compression of the adrenal glands [thus increasing the secretion] is followed by glycosuria; while their exclusion, by extirpation or ligation of their vessels, is followed by a considerable fall of the sugar-content of the blood." Kaufman[207] found, moreover, that ligation of the inferior vena cava caused a rapid diminution of sugar both in normal glycæmia and in glycosuria. We have seen that it is in the blood of this great vessel that the adrenals secrete their product.

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[197] Schäfer: *Loc. cit.*, vol. i, pp. 926, 927.
[198] Chauveau and Kaufmann: C. r. de la Soc. de biol., p. 29, 1893.
[199] Landois: *Loc. cit.*, p. 315.
[200] Kaufmann: C. r. de la Soc. de biol., p. 284, 1894.
[201] Blum: Deutsch. Archiv f. Med., Bd. lxxi, Nu. 2 u. 3, S. 146, 1901.
[202] Croftan: Amer. Med. Jan. 18, 1902.
[203] Metzger: Münch. Med. Woch., Bd. xlix, S. 478, 1902.
[204] Herter: Med. News, Oct. 25, 1902.
[205] Herter: Amer. Med., May 10, 1902.

This evidence, in the light of the facts previously submitted, speaks for itself: Acromegaly gives rise to glycosuria because the diseased organ, the anterior pituitary, stimulates excessively the adrenals, the secretion of which has been shown experimentally to cause glycosuria. This affords additional proof to the effect that the adrenals are governed by the anterior lobe of the pituitary body through the intermediary of a direct nerve-path.

On the whole, the evidence presented in the present section appears to me to warrant the following postulates:—

1. *The thermogenic (or heat) center and the respiratory (or polypnœic) center are not, as believed by some observers, located in the tuber cinereum, the bulb, or the spinal cord, the thermogenic areas in these regions being but subsidiary centers—if anything but thermogenic nerve-paths—of which the bulbar are the most important.*

2. *The thermogenic center is located in the partition between the two lobes of the pituitary body, and in mammals is the highly developed homologue of the test-organ or osphradium of lower forms. As such it is the governing center of the adrenals, its nerve-path to these organs being as follows: from the test-organ to the posterior lobe of the pituitary and thence upward to the tuber cinereum; along this structure to the pons and bulb, and down the spinal cord to the first, second and third dorsal*

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[206] Herter and Wakeman: Amer. Jour. Med. Sci., Jan., 1903.
[207] Kaufmann: Arch. de physiol., T. viii, p. 150, 1896.

nerves; thence to the sympathetic chain; down this chain to the greater splanchnic nerves in which it reaches the suprarenal plexus and through it the adrenals.

3. *The respiratory center is located in the posterior or neural lobe of the pituitary body and represents therein the aggregate of nuclei which are themselves the chief centers of all the cranial nerves that govern the respiratory muscles.*

4. *The nerve-chains from the respiratory center pass upward to the supra-infundibular nucleus, and thence posteriorly to the bulb, where they become merged with the (subsidiary) centers of the various cranial nerves which govern the functions of the respiratory muscles.*

Jacques Loeb's prediction that "through the oxidases one may in time be able to control life as the artist governs the keys of the piano," and his belief that "not merely the normal course of life, but also that vast gamut of diseases characterized by metabolic derangements, might be controlled if we only knew how to favor or retard the action of the oxidases," are afforded a foundation in the views submitted in the present and foregoing chapters. Selecting only out of the various functions I have pointed out those that bear directly upon this feature of the general problem, this foundation may be said to consist of the following facts:

1. Adrenoxidase is an aggregate of the body's oxidases, and the dynamic principle in metabolism and therefore of the vital process. It follows, therefore, that *adrenoxidase (the oxidases) is the agent through which life may be controlled.*

2. Adrenoxidase is the oxygen-laden secretion of the adrenals, while these organs are, in turn, governed through a nerve-path whose center is located in the pituitary body. Hence, *it is the center of the adrenals in the pituitary body which, through the adrenals and their adrenoxidase-forming secretion, controls life.*

3. The adrenal center is primarily a sensory organ and the homologue of the "test-organ" which in the lower chordata serves to test the "respiratory fluid" and thereby to protect these animals "against the intrusion of noxious substances." As in the higher chordata, including man, the "respiratory fluid" is the blood, it follows that *the adrenal center is an organ having for*

its purpose to test the blood and protect it against the intrusion of noxious substances.

4. Adrenoxidase embodying, as it does, the ferment of ferments, it is the dynamic principle of tissue metabolism. The proportion of adrenoxidase in the blood being governed by the adrenal center, it follows that *noxious substances introduced into the blood can, by provoking a reaction of the adrenal center, enhance the activity of metabolic processes.*

5. While the adrenal center is the thermogenic or heat center, adrenoxidase, as the dynamic principle of metabolism, supplies the oxygen which, by combining with the phosphorus of nucleins, liberates the bulk of the body's heat energy. Fever being the expression of an excess of heat energy thus produced, the adrenal center is also the governing center of the febrile process. It follows *that inasmuch as we can therapeutically increase or abate fever, we can also control tissue metabolism and its derangements and defend the body against disease.*

CONCLUDING REMARKS.—The more recent literature has contributed experimental data which further sustain all the foregoing conclusions.

Keeton and Becht[208] having caused *hyperglycemia* in dogs by stimulating the pituitary found that it ceased when the spinal cord was transected at the level of the second thoracic vertebra and after section of the splanchnics. The hyperglycemia persisted, however, after section of the nerves in the hepatic pedicle where the nerve supply to the adrenals is not interfered with. The authors, therefore, conclude that the phenomenon is due to the presence of a nervous pathway through the splanchnic nerves to their terminations in the adrenals.

Again, Lépine[209] found that *polyuria* or *diabetes insipidus* could be caused by severing the splanchnic nerves which contain the secretory fibers to the adrenals. Now, Camus and Roussy[210] referring to the same disorder, write as follows: "The important fact is that a superficial lesion of the base of the brain, often involving only the surface and produced involuntarily in the removal of the pituitary body, is followed by polyuria. In our animals it seems that the opto-peduncular region alone marks the zone within which a lesion is followed by polyuria. It lies at the level of the grey substance of the *tuber cinereum* in the vicinity of the infundibulum." We have seen that it is precisely through the infundibulum and the tuber cinereum that I traced the fibers from the pituitary to the adrenals. In the experiments mentioned, the lesions deep or slight caused a local inflammatory process which prevented the passage of impulses from the pituitary to the adrenals, causing polyuria as had Lépine when he severed the splanchnics.

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[208] Keeton and Becht: Amer. Jour. Physiol., xlix, 248, 1919.
[209] Lépine: Sajous's Anal. Cyclopedia of Pract. Med. ii, 484, 1899.
[210] Camus and Roussy: Endocrinology, iv, 507, 1920.

Finally Newmark[211] reported the case of a boy of fourteen years in which *diabetes insipidus* had existed five years. At the autopsy there was found among other lesions destruction of the posterior or nervous lobe of the pituitary and nearly all the pars intermedia to which lesion the author attributes the diabetes insipidus. Obviously here, in the light of my foregoing statement, the polyuria was also due to arrest of the pituitary impulses to the adrenals.

The autopsy confirmed another important fact. We have seen that an olfactory area-like membrane, through nerve paths in the tuber cinereum, bulb, cord, etc., excites abnormally the thyroid, adrenals, and pancreas and indirectly the phagocytogenic organs, and causes the production of an autoantitoxin calculated to break down poisons. Now, in Newmark's case, the pars intermedia, which contains this *test-* or *immune- membrane* was nearly all destroyed. The boy could not only drink wine in large quantities and several quarts of beer—a greed for fluids accounted for by his diabetes insipidus—without showing the slightest degree of intoxication, but whiskey likewise. The wine and beer might be excluded owing to their small content in alcohol—about 5 to 12 per cent. by volume on an average—but the whiskey which contains from 45 to 55 per cent. as a rule was certainly an intoxicant. Why should the child have shown no intoxication? Merely because being deprived of his test-organ his adrenals failed to be stimulated and to increase the oxygenation of the blood which under normal conditions would have caused the alcohol to be actively oxidized—the underlying cause of "intoxication" as will be shown in the Section on Alcohol (p. 1326). Such cases are rare, but the few available have emphasized the importance of the test-organ in immunity and therapeutics.

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[211] Newmark: Archives of Int. Med., xix, 550, 1917.

CHAPTER XVII.

THE LEUCOCYTES, PITUITARY, THYROID, PARATHYROIDS, AND ADRENALS, AS THE FUNDAMENTAL ORGANS IN PATHOGENESIS, IMMUNITY AND THERAPEUTICS.

THE LEUCOCYTES AS THE DISTRIBUTORS OF REMEDIES AND POISONS.

We have now seen in the foregoing pages that considerable evidence sustains my view that the pituitary body as central sympathetic ganglion governs[1] the body's auto-protective or immunizing mechanism, and that by means of our remedies its functional activity could be enhanced at will, and thus caused to activate the antitoxic properties of the blood. An eminent French clinician, Hayem,[2] once remarked: "Therapeutic weapons are wanted which will *reinforce the defensive power of the organism* by increasing the functional activity of the leucocytes or by developing chemical antidotes"—the trend of our day being in harmony with Hippocrates's belief in the *vis medicatrix naturæ.* That this is precisely the underlying thought of my own doctrine is self-evident; but it does what no other doctrine has done: it points to the identity of Nature's mechanism and to the means she adopts to attain her object.

We have reviewed the main features of this mechanism. We have seen that the pituitary contains a test-organ related by nerve-paths with the adrenals, which in turn govern, through their secretion, the activity of all metabolic processes in the blood as well as in the tissues. As the thermogenic center, this test-organ also presides over the febrile process—which is but an exacerbation of catabolic activity, raising it when need be—to destroy, not only tissue-wastes, but all toxic substances which adventitiously gain access to the blood-stream. The process through which the protective activity of the test-organ is awakened suggests itself as the next question in point, but before it can be taken up an important feature must receive attention, viz., the manner in which the substances which provoke this reaction enter the blood and reach the tissues. As drugs and poisons are identical as far as the test-organ is concerned—both being noxious agents—the absorption and distribution of drugs will serve to illustrate the same processes in the case of poisons.

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[1] Sajous: Monthly Cyclo. of Pract. Med., Jan., 1903; Phila. Med. Jour., Mar. 7, 1903.

[2] Hayem: Presse médicale, Aug. 12, 1903.

We have seen that leucocytes take up food-products from the intestine to convert them into granulations which they carry to all tissues and deposit therein. I showed furthermore, in the fifteenth chapter, that these granulations not only penetrate all cells, but that they become part of their structure. That ingested drugs or poisons should also be taken up from the intestinal canal by leucocytes and distributed to the various tissues is shown by the fact that MacCallum traced leucocytes which had englobed albuminate of iron in the intestine to the spleen, liver, etc., an experiment repeated successfully by other investigators with proteids and other food materials. This applies as well, as far as distribution is concerned, to drugs injected subcutaneously or directly into the blood: they are more or less promptly engulfed or absorbed by leucocytes and distributed to various parts of the organism.

"Recent experiments in France show," says an editorial writer,[8] "that leucocytes fulfill a very important function in distributing medicinal drugs to all parts of the body. . . . This is shown by various experiments. Here, for instance, is a rabbit under whose skin is injected a little strychnine or atropine. At the end of, say, half an hour, some of the blood is drawn off and divided by centrifugal treatment into its three parts—leucocytes, red globules, and plasma. Equal quantities of each are injected into three animals, and it is seen that the one that receives the leucocytes is poisoned, while the others are not. The leucocytes transfer these drugs from one part of the body to another, and this is their greatest utility. It is the more so that the place where they transport these substances varies according to circumstances. In normal conditions—that is, in health—the leucocytes carry the drug to the liver and marrow. In illness they carry it to the affected points, to the centers of irritation, where the arrival of the leucocytes is most desirable. . . . . But we can depend on them to carry iron to the blood-making organs, iodoform to tuberculous lesions, salicylate of soda to affected points, etc. . . . . There is another fact that must be taken into account: the leucocytes, it is true, carry drugs to affected points, but they carry them also, with special insistence, to certain organs. Different organs attract different drugs; the liver, iron; the thyroid gland, arsenic and iodine; while the skin, the spleen, the lymphatic ganglia, and other organs seem to constitute regions of choice for several chemical substances." Indeed, Morel[4] found that finely powdered nux vomica was engulfed by leucocytes as well as any other substance foreign to the blood. Besredka,[5] having injected a soluble salt of arsenic into rabbits, found analytically that while the red cells and the plasma contained none, the leucocytes had absorbed it. Silver salts also were found to be ingested by leucocytes by Samoïloff.[6] Montel[7] obtained a similar result with sodium salicylate. Lombard[8] obtained corresponding results with atropine and strychnine. Marcel Labbé and Lortat-Jacob[9] injected iodides subcutaneously and into the peritoneum and found that leucocytes absorbed these salts. Calmette obtained similar results with atropine; Metchnikoff, with soluble iron; Stassano, with mercurial salts; Neisser, with an oleate of calomel; Carles,[10] with ferrous iodide and other preparations of iron, colloidal silver, morphine, olive oil, rhubarb, and biniodide of mercury; Lancelin[11] and Lombard, with morphine, etc.

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[8] Editorial: Cleveland Med. and Surg. Reporter, Aug., 1904.

Can we accept as sound, however, the belief that leucocytes modify their itinerary, so to say, when a given area is diseased and carry to that area drugs that may be beneficial to it? M. Labbé[12] states that "while cinnabar injected into the circulation is, in normal animals, taken to the liver, the bone-marrow, etc., (Cohnheim, Ponfick, etc.), in diseased animals it is deposited in the morbid foci (Schüller, Ribbert, Orth, Wyssokowitch)." It is upon this principle that Landerer based his theory that sodium cinnamate reached the pulmonary foci in tuberculosis; that mercury is believed to seek out syphilitic eruptions, that iron adjusts itself to hæmatopoietic organs in anæmia, that iodoform proceeds at once to tubercular regions, that sodium salicylate selects the joints, etc. The drug-laden leucocyte is, according to this view, capable of intelligently and wilfully selecting the area to which it is to proceed; or, it can be drawn to the morbid focus through chemiotaxis; or, again, owing to the vulnerability of such a focus to bacterial invasion, it can be attracted thereby, as are other phagocytes, irrespective of their contents. Analysis of the question shows that while there can be no doubt that leucocytes take up drugs as they do any useless or noxious agent that appears in the blood, the belief that they are specifically attracted to any diseased focus because they happen to contain a substance that may be beneficial to it is erroneous.

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[4] Morel: "Recherches expérimentales sur les leucocytes," Paris, 1892-93.
[5] Besredka: Ann. de l'Inst. Pasteur, T. xiii, pp. 49, 209, 1899.
[6] Samoïloff: Lubarsch u. Ostertag, "Ergebnisse der allg. Path., etc.," Bd. iv, S. 197, 1899.
[7] Montel: "Thèse de Bordeaux," 1900-1901.
[8] Lombard: Thèse de Paris, 1901.
[9] Marcel Labbé and Lortat-Jacob: C. r. de la Soc. de biol., July 4, p. 830, 1903.
[10] Carles: "Du rôle des leucocytes dans l'absorption, etc.," 1904.
[11] Lancelin: Thèse de Bordeaux, 1902.
[12] M. Labbé: Presse médicale, Aug. 10, 1904.

The observations of Schüller, Ribbert and others, that cinnabar, which, in normal animals, is distributed in the liver, bone-marrow, etc., is deposited in the morbid foci in diseased animals, only prove that local leucocytosis has occurred—a common phenomenon observed even in the absence of any drug in the organism. This means only that leucocytes laden with the drug in more or less great numbers are diverted from their normal haunts to invade the diseased area to act as phagocytes, to sustain nutrition, rebuild tissue, etc. That the drug-laden leucocytes travel everywhere is moreover shown by the fact that in the experiments of Lombard, Calmette and Besredka, the blood examined was taken from the *general* circulation, and its leucocytes were found to contain the drugs injected. On the other hand, Landerer,[13] referring to Schüller, states that "he found cellular deposits in *predominating* numbers in inflamed or injured areas," simply meaning thereby an excess of leucocytes as compared to other regions.

A very interesting phase of the problem presents itself in this connection, viz., additional proof that leucocytes secrete the products they absorb as they do their nucleo-proteid granules in the tissues—drugs, more or less modified, replacing the nutrient particles, and being secreted automatically in lieu of the latter.

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[13] Landerer: "Le traitement de la tuberculose," 1899.

Carles[14] injected subcutaneously fine grains of carmine in the leg of a frog, then cut slightly the foot of the opposite side and introduced small pieces of glass in the wound. Fifteen hours later the latter was found to contain a large number of leucocytes stuffed with carmine. Another incision on the opposite side, led to a similar result after twelve hours. This experiment was repeated several times with the same result, the injections being made in different parts of the body. Carmine-laden leucocytes were also found in the liver. Cohnheim resorted to the same procedure forty years ago; carmine injected in the lymphatic sac of frogs appeared in the leucocytes in an ulcerated cornea. Carles then tried the experiment with sulphide of mercury and collargol, with the same result. He attributes these phenomena to chemiotaxis; but interpreted from my standpoint, it is due, as stated above, to a less obscure process, *i.e.*, the *function* of the leucocytes to carry to the tissues as nutrient material, whatever they absorb and digest, and in greater quantities to diseased tissues to facilitate the process of repair.

This is further shown by the fact that leucocytes migrate through the walls of vessels to reach the tissue-cells and deposit their load therein, whether this be composed of nutrient granules or a drug. Thus Stassano and Billon,[15] after injecting lecithin in frogs, observed a profuse leucocytosis of cells laden with this substance. "A curious fact, however," says Carles, referring to this experiment, "is that leucocytes containing lecithin are also found outside the vessels. As true alimentary carriers they drop their charge, therefore, in the various tissues in order to nourish them; they even reach those that are deprived of capillaries thanks to diapedeses"—precisely as I had stated the previous year.

The leucocytes may be killed, however, by the drugs they absorb. Alluding to powdered drugs of various kinds, Carles states that "they take them up as well as any other inert substances, but that they subsequently die without rejecting them," as observed by Morel with powdered nux vomica. Carles noted a similar effect with rhubarb.

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[14] Carles: *Loc. cit.*
[15] Stassano and Billon: C. r. de l'Acad. des sciences, p. 623, 1902.

That the substances or drugs absorbed by the leucocytes that are harmless to them are actually secreted by them in the tissues was first observed by Schüller, who, as stated, observed that they deposited a larger quantity of their contents in diseased areas than elsewhere, solid elements being reduced to a state of extreme division. M. Labbé[16] also states that "insoluble drugs are absorbed and dissolved in the leucocytes" as shown by their influence on calomel and arsenic. Besredka, having provoked tuberculous abscesses in rabbits, then injected arsenic into the animals at intervals. He found the drug not only in the leucocytes, but also in the pus of the abscesses. Carles repeated these experiments and obtained similar results; he found that mercury and copper followed the same course as the arsenic—a fact, by the way, which emphasizes the absence of specificity as far as the distribution of the drugs is concerned. That the leucocytes secrete their granulations (Hankin, Kanthack, Hardy and Keng, Ehrlich, Hardy and Wesbrook, and others) explains how these drugs, irrespective of those derived from broken-down cells in the pus, are deposited in the tissues—precisely, I may add, as if they were nutritive particles.

Pathogenic organisms may likewise be transported by leucocytes to any part of the body and initiate morbid processes. Four years ago,[17] in an article opposing Koch's views concerning the non-infectivity in man of bovine tuberculosis, I emphasized the fact that direct infection of the lungs can occur through bacilli ingested by leucocytes in the intestinal canal, and reached the conclusion that "contaminated milk and foods are, therefore, as active sources of infection as air-borne germs." As is well known, the bacillus of tuberculosis is pathogenic when dead, and the endotoxin is liberated when the germ is disintegrated. Landerer, referring to Schüller's observation[18] that the contents of leucocytes were deposited in relatively large quantities in inflamed or injured tissues, states that these observations were confirmed as to bacteria by Ribert, Orth and Wyssokowitch. Carles, who mentions these authors, writes in this connection: "Recently acquired knowledge of the physiology of leucocytes explains the predisposing rôle of traumatism as to the localization of Koch's bacillus. The staphylococcus (Wyssokowitch, Orth, Weichselbaum), the pneumococcus (Netter, Banti, Vanni), and many other microörganisms have since been found to have the same tendency to invade the damaged areas owing to the chemiotactic power of the leucocytes which had ingested them. This fact has been placed beyond question by numerous confirmatory clinical and experimental facts (Gabbi, Tournier and Courmont, Chauveau, Rosenbach, Becker). Widal and Ravaut[19] witnessed a case in which a tuberculous focus thus became infected by the bacillus of Eberth, etc.—all due doubtless to imperfect phagocytosis or to the death of the leucocytes containing living bacteria, or dead bacteria containing endotoxins. Many examples of this kind are available in literature, as every one knows.

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[16] M. Labbé: *Loc. cit.*

[17] Sajous: Monthly Cyclo. of Pract. Med., Jan., 1908; Phila. Med. Jour., Mar. 7, 1908.

[18] Landerer: *Loc. cit.*

Can we say in the face of this evidence that leucocytes carry drugs to the diseased sites, where their arrival "is most desirable"? If such were the case, how could we account for the distribution of bacteria and for inert substances to the same regions? That substances such as iron, arsenic, iodide, phosphorus, etc., which fulfill a physiological rôle in the organism are taken by these cells to the tissues where they are stored, or back to the intestinal canal for elimination if they are not required, is doubtless true, but that agents such as mercury, sodium salicylate, atropine, opium, strychnine, etc., which are totally foreign to the tissue elements, should accumulate in any morbid tissue otherwise than as a result of the local leucocytosis that attends all morbid processes seems illogical. This is an important feature from the standpoint of therapeutics, for while some advantage may be derived from the use of appropriate remedies because they must reach the diseased area through the intermediary of the leucocytes, this does not represent, as the authors who have studied the leucocytes in this connection seem to believe, the manner in which drugs—including those known to be carried to the morbid tissues—produce their main physiological effects.

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[19] Widal and Ravaut: Soc. méd. des hôpitaux, Jan., 1902.

This is further shown by the fact that the effects of most drugs (the exceptions being those such as iron, phosphorus, etc., which form part of our tissues) are produced mainly through their action on the central nervous system.

Digitalis, for example, is thought—irrespective even of any participation of the leucocytes in the process—to act directly upon the heart muscle, but Traube, in 1871, showed that transsection of the cord high up annulled its effects, and Boehm[20] found that the same procedure arrested its action when it had become manifest. This indicates plainly that the action of the drug is not direct, *i.e.*, on the heart-muscle itself. This may be shown in another way. Hebdom,[21] for instance, found that digitalin acted on an isolated heart when a 1 to 50,000 solution was used. But can we assert that a corresponding dose in man will act in the same way? The minimum estimate of the quantity of blood in the body of an adult is 13 pounds; *i.e.*, 100,000 minims. This quantity would thus have to contain a *full grain* of digitalin to react directly upon the heart, granting that no waste occur either in the stomach, intestines, liver, or blood, before reaching that organ. Now, $^1/_4$ grain of Merck's digitalin, according to Wood,[22] "represents the full therapeutic dose." In the blood this would make a solution of 1 to 400,000, which is inactive on the detached heart. Again, if the view that the drug acts directly on the heart-muscle were sound, the hypodermic use of a sufficient quantity to make Hebdom's 1 to 50,000 solution should at least be required. In truth, a dose thus administered and making a solution in the blood *but one thirty-second as strong* as this, is a powerful one. Thus, Deucher[23] found that a dose of digitalis given hypodermically produced the same effects as a dose four times as great administered by the mouth. Inasmuch as $^1/_4$ grain of digitalin is stated by Wood to produce the full therapeutic effects of the drug, $^1/_{16}$ grain should thus provoke equivalent effects hypodermically. This is equal to a 1 in 1,600,000 solution in the blood mass. And yet this does not allow for the diminution of the dose in the latter. Can we consistently admit, in view of the antitoxic properties of the blood (especially active in the leucocytes) which underlie immunizing processes now engaging the attention of the whole scientific world, that a glucoside will suffer no chemical change? Even if defibrinated blood-serum be used as a menstruum for digitalin in experiments, such as Hebdom's, on the isolated heart, the environment of the drug is greatly modified through the absence of blood-cells, fibrin, etc. Thus, variation of temperature provokes precisely contrary effects. Masi showed that, while digitalin arrests the frog's heart in *systole* at the normal temperature, at a lower one it arrests it in *diastole*. Moreover, how do we know that the supposed direct action of the drug will always manifest itself on the mammalian heart as it does experimentally on the batrachian? Masi found that at identical temperatures digitalin arrested the frog's heart in diastole and the mouse's heart in systole. All this shows distinctly that the prevailing view that digitalis acts directly on the heart cannot bear close scrutiny. Indeed, the action of this drug has remained obscure. "In our experiments upon the mammalian heart," writes H. C. Wood,[24] "we have seen in the final acts of digitalis drama happenings so curious and unexpected that at present no proposed theory as to the action of the drug is sufficient."

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[20] Boehm: Arch. f. gesammte Physiol., Bd. v, S. 153, 1872.
[21] Hebdom: Skand. Arch. f. Physiol., Bd. vii, S. 169, 1896; Bd. ix, S. 1, 1899.
[22] Wood: "Therapeutics," eleventh edition, 1900.
[23] Deucher: Deutsches Archiv f. klin. Med., Bd. lviii, S. 47, 1897.

The drugs which, as shown in the foregoing pages, are distributed by leucocytes—excepting as stated, agents which take part in general nutrition—also produce their main effects through the central nervous system. Thus, Cushny[25] states that "*atropine* acts as a stimulant to the central nervous system and paralyzes the terminations of a number of nerves." Of the aromatic series to which the *salicylates* belong, he also says: "They are all possessed of a more or less marked action on the central nervous system." Wood,[26] referring to *strychnine*, writes: "The fullest permissible doses stimulate very powerfully the respiratory centers, and also slightly increase blood-pressure by stimulation of the vasomotor centers and probably also of the heart itself." Of *silver*, the same author says the symptoms of poisoning are "those of gastro-enteritis with violent disturbance of the nervous system due to a direct action of the poison upon the cerebrum and the spinal cord." He also states that "sometimes the influence of *mercury* falls almost exclusively upon the nervous system, and produces a peculiar train of paralytic phenomena." In his section on opium (we have seen that leucocytes were found to carry morphine to the tissues), Wood says: "It is undoubtedly a stimulant to the spinal cord; but . . . . the cerebrum in man is so infinitely more susceptible to its influence than is the spinal cord that this spinal effect is rarely perceptible in man." The physiological action of morphine emphasizes strongly the question in point, for although taken up and carried by leucocytes to all parts of the organism, it is only through its action on the central nervous system that its effects, including the relief from pain, are produced.

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[24] Wood: *Loc. cit.*

[25] Cushny: "Pharmacology and Therapeutics," fourth edition, 1906.

[26] Wood: "Therapeutics," twelfth ed'tion, 1905.

A still more striking example of this fact is the physiological action of the coal-tar antipyretics and analgesics, antipyrin, acetanilid, etc. Although these drugs are widely used in practice, their action, as stated by Cushny,[27] "is very imperfectly understood." Now, Sawadowski[28] showed that removal of the brain *above* the basal ganglia, the optic thalami and the striated bodies did not prevent the action of antipyretics. He found, however, that when these ganglia were detached from the lower part of the spinal system, the antipyretics no longer reduced fever. An important fact imposes itself in this connection, viz., the experimental incision inevitably destroyed the nerve-paths from the pituitary body to the upper spinal structure, and, therefore, the nerve-path connecting it with the adrenals.

This evidence, supplemented by that submitted in the first volume and in the preceding chapter, seems to me to warrant the following conclusions: (1) *that leucocytes, acting as phagocytes, absorb not only food-products in the alimentary canal and in the blood-stream, but also drugs, poisons and pathogenic organisms;* (2) *that whatever substance a leucocyte engulfs or absorbs, including pathogenic elements, is submitted therein to*

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[27] Cushny: *Loc. cit.*, p. 373.

[28] Sawadowski: Centralbl. f. med. Wissensch., Bd. xxvi, S. 145, 161, 1888.

whatever action its digestive constituents may have on that substance, the product being secreted broadcast in the tissues as if it were invariably a nutritive substance; (3) *that if the intracellular digestive process be imperfect or if the leucocyte be killed by them, living pathogenic bacteria may thus be disseminated by leucocytes;* (4) *that drugs and poisons more or less modified chemically, dissolved, or triturated in the leucocytes, may thus be distributed by them to all tissues;* (5) *that while in some instances this may cause remedies capable of promoting local resolution to reach diseased areas—especially in view of the local leucocytosis of which such areas are the seat—this does not represent the process through which drugs, poisons, and bacterial toxins and endotoxins produce their main physiological effects;* (6) *that these physiological effects and the beneficial influence of remedies are due mainly to their action upon the central nervous system.*

THE ANTERIOR PITUITARY AS A LYMPHOID ORGAN IN WHICH THE PRODUCTS OF LEUCOCYTES AND ANY DRUG, POISON OR TOXIN THESE CELLS MAY CONTAIN ARE EXPOSED TO THE TEST-ORGAN.

In the preceding chapter I referred to the anterior lobe of the pituitary body as an "organ of special sense," owing to the presence therein of a sensitive organ which I assimilated to the "test-organ" found by zoölogists in Tunicata, the lower Chordata and other animals far down in the phylogenetic scale. Spengel, who first described the structure in these ancestral forms, referred to it as an "olfactory organ" and concluded that its function was to test the water which supplied them with oxygen—a view now generally accepted by zoölogists. Gentès, we have seen, though unaware of the fact that I had attributed functions similar to those of the test-organ to the anterior pituitary body—and probably of the views of zoölogists regarding it—found, in the partition separating it from the posterior lobe of the higher mammals, cat, dog, etc., a sensory organ which could also have been termed an "olfactory organ," since its cellular elements recalled "precisely," he said, those of the olfactory area of the nasal mucous membrane. The data contributed by zoölogists, my own—based on clinical, physiological and histological investigations—and those contributed by Gentès, harmonize therefore in attributing to the anterior pituitary body—including its posterior wall—besides the functions its epithelial elements subserve, the rôle of a sensory organ. It is evident, therefore, that my opinion that the purpose of this organ is to afford some form of protection to the organism, harmonizes fully with the teachings of several branches of biological science.

In the higher animals, however, we are no longer dealing with a structure which, as in the sea-squirt, the mussel, the lancelet, etc., tests in-going sea-water; and as their "respiratory fluid" is the blood, it follows that whatever protection the test-organ affords in these higher vertebrates, including man, must have for its purpose to counteract the effects of poisons brought thereto by the blood. Indeed, as stated by Claude Bernard, the blood of vertebrates "is an internal medium in which the anatomical elements live as fishes do in water."[29]

Again, the protection afforded by the test-organ in the invertebrates is far-reaching not because the oxygen derived from their respiratory fluid is materially reduced when noxious materials are present in it, but because this fluid also brings them their food. Thus, Amphioxus buries its body in the sand, the mouth and its cirri protruding in the water above. The latter, which supplies it with its oxygen, also brings microscopic plants and débris, which pass downward into the slimy secretion of its pharynx, while the water passes out again through the gill-slits, the respiratory organs. The test-organ is so situated, however, that any noxious substance entering either the respiratory or digestive apparatuses of the animal comes into contact with it. It is evident that the purpose of the test-organ is not so much to protect the animal against toxic agents that compromise the purity of the water as a respiratory fluid but as a nutritional medium.

This apparently militates against the fact that in the higher animals the blood replaces the sea-water as regards its functional relations with the test-organ of the pituitary body, since, in the light of the views I have advanced, it is not the plasma which contains proteids and other food-stuffs, but the leucocytes. The situation would seem further complicated by the fact that, as shown in the preceding section, poisons as well as foods are absorbed in the intestinal canal and in the blood by these cells, and distributed by them throughout the organism. If, as in the invertebrates or ancestral vertebrates provided with a test-organ and a water vascular system, poisons must come in contact with the test-organ, in the higher vertebrates provided with a blood vascular system, the leucocytes would have to *enter* the pituitary body and secrete their toxic principles therein. That these cells, *i.e.*, leucocytes laden with poisons, food-products, etc.—can penetrate into the anterior pituitary is shown in the annexed illustration of a section of this organ, borrowed from a very able work by Professor P. E. Launois, of Paris,[30] and intended to show the presence of fat globules (a normal result, from my viewpoint, of the fact that they ingest *fats* in the intestinal villi) in what he describes as "polynuclear leucocytes of the blood in the intra-parenchymatous capillaries." It is obvious, therefore, that at least some of the leucocytes whose function it is to absorb food-substances, poisons, etc., anywhere in the body enter the anterior pituitary body.

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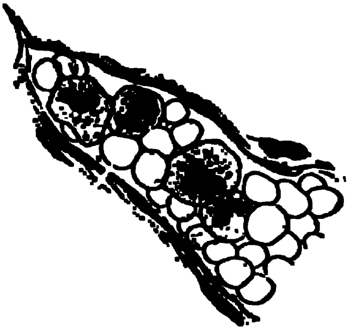
[29] Claude Bernard: "Leçons sur les propriétés des tissus vivants," pp. 55 to 58, 1866.



POLYNUCLEAR LEUCOCYTES IN THE INTRAPARENCHYMATOUS CAPILLARIES OF THE ANTERIOR PITUITARY. (*Launois.*)

What is the nature of their relationship with the test-organ? How can this structure become influenced by the relatively small number of peptone- or poison-laden leucocytes which, merely as casual cellular constituents of the blood, happen to circulate in this organ? Before these questions can be answered, certain features of the prevailing views concerning the functions and histology of the anterior pituitary body require attention.

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[30] P. E. Launois: "Recherches sur la glande hypophysaire de l'homme," Paris, 1904.

The anterior pituitary is now considered as a secreting gland, capable, as are the thyroid and adrenals, of furnishing a secretion to the blood. In the light of my views, however, this rôle no longer belongs to the pituitary body in all animals provided with adrenals, since I regard these organs as offshoots, so to say, of the anterior pituitary, which assumed at a given time in the animal scale all the secretory functions of the latter. Whether the adrenals, as in Sauropsida, be closely connected with the gonads, in Amphibia with different parts of the mesonephros, in Teleosts either with the latter or with the degenerate pronephros, etc., or as in the higher vertebrates, including man, with the fully developed kidney, the adrenals are invariably connected by a nerve path with the anterior pituitary—through, we have seen, the posterior or neural lobe, with which it becomes merged during embryological development. The purpose of this union asserts itself in view of the fact—pointed out in the preceding chapter—that the neural lobe is the seat of the sympathetic and other motor centers which have as their purpose to connect the test-organ with the nerve-center through which its defensive functions (as regards the body at large) can be carried out, namely, the adrenal center.

These facts suggest and additional evidence will show, (1) that the anterior pituitary body is not a secretory organ, and (2) that its function, as previously emphasized, is to test the quality of the blood circulating through it and awaken, if need be, a defensive reaction throughout the body. Such being the case, the supposed "secretory" elements of the anterior pituitary cannot be such. This is further suggested by the arrangement and structure of the epithelium.

If the organ were a gland, its secreting elements should be arranged in regular rows as in other glands, but such is not the case. As is well known, the anterior pituitary is made up of convoluted tubes or alveoli. In these structures, the cells,

Fig. 1.

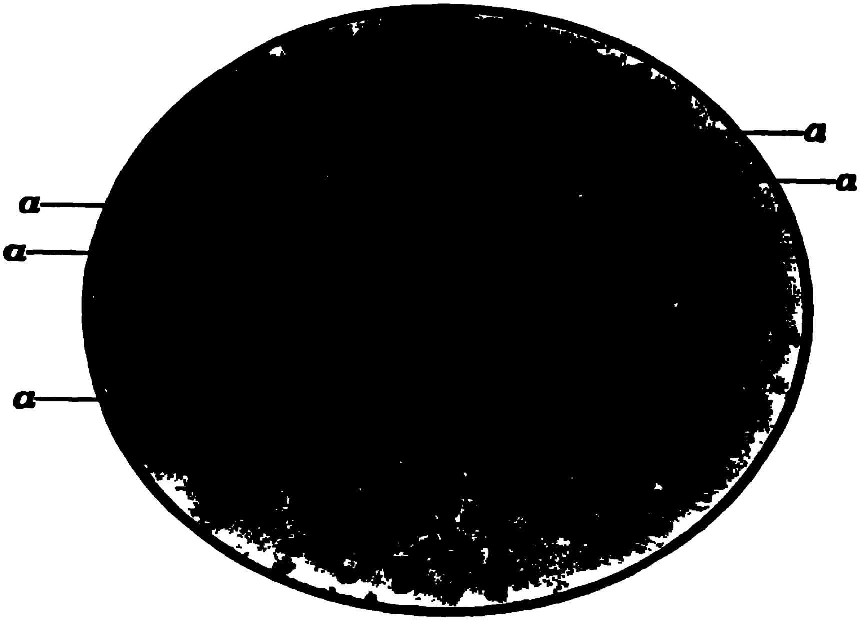
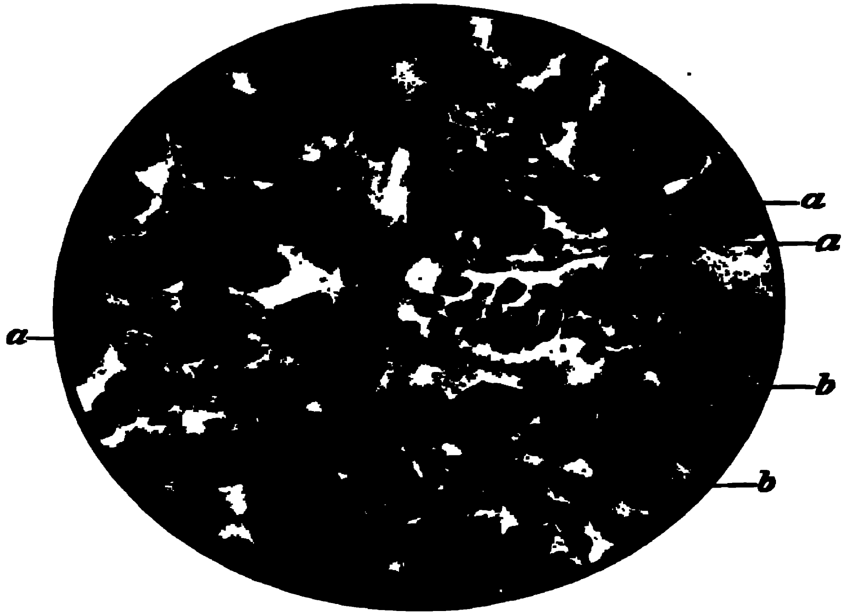


Fig. 2.



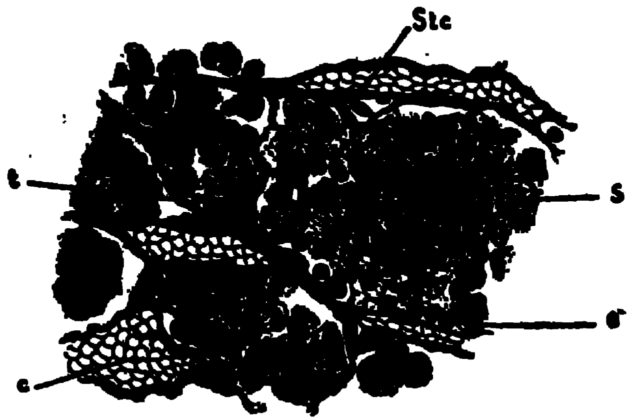
THE EPITHELIUM OF THE ANTERIOR PITUITARY AS PARTLY COMPOSED OF PHAGOCYTIC EPITHELIOID CELLS. *[Sajous.]*

Fig. 1, Epithelioid cells in a tuberculous lymphatic gland a.

Fig. 2, Normal tissue of anterior pituitary. Phagocytic epithelioid cells a.

[illegible] and there arranged in order, owing to the [illegible] tubular walls of stroma, are massed promiscuously. This is made clear by the cut reproduced below, from a paper by Launois and Mulon,[81] which shows according to their description, "siderophile" and "eosinophile" cells. In fact, Launois specifically states that they are simply groups of cells between which a secretion is formed. The microphotograph opposite page 1046 likewise emphasizes this important fact.

On the other hand, there is a striking resemblance between the large mononuclear cells which constitute the supposed glandular epithelium of the organ and the phagocytic endothelioid cells found, for instance, in the mesenteric lymph-glands. To emphasize this resemblance I submit herewith two microphotographs, one of an aggregate of such lymphatic endothelioid cells from a case of tuberculosis of the peritoneum (Fig. 1); and one of normal tissue from the anterior pituitary (Fig. 2). Indeed, the morphological structure of the pituitary is such as to have caused it to be compared to a lymph-gland by the older investigators, Monro, Müller[81a] and others. Nearer, however, to my own interpretation, is that of Charles Robin,[81b] who, in 1860,



IRREGULAR AND PROMISCUOUS DISTRIBUTION OF CELLS IN THE STROMA. *Ste*, Intercellular stroma. *t*, Offshoots from the stroma. *c*, Blood capillaries. *s*, Siderophile cells. *e*, Eosinophile cells.

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[81] Launois and Mulon: Annales de gynéc. et d'obstet., Jan., 1904.

[81a] Müller: Jenaische Zeitsch. f. Naturw., Bd. vii, S. 327, 1872.

[81b] Charles Robin: "Dictionnaire Encyclo. des Sc. Méd." art. "Lymphatiques," 1860.

specified that the pituitary body did not actually form part of the lymphatic system, but that it was a lymphoid organ.

From my standpoint, however, this applies only to the anterior lobe. As is well known, it is bean-shaped and the posterior lobe is incorporated into its hilum. Böhm, Davidoff and Huber[31c] state, referring to lymph-glands, that "in shape they are much like a bean or kidney and the indentation on one side is known as the hilum." Both the anterior pituitary and the lymph-gland have a fibro-elastic capsule, septa which divide the organ into a multitude of compartments to which the above-named histologists refer as "medullary cords" (just as Launois calls the tubules of the anterior pituitary "cords"). Both contain lymph-sinuses. As shown below, the anterior pituitary also contains what in the lymph-gland Toldt termed a "terminal sinus," lined throughout with endothelial cells, which are continuous with those of the afferent and efferent lymph-vessels,"—the afferent vessels being omitted in the pituitary. It is not strange, therefore, that we should find the great phagocytic mononuclears in the anterior pituitary. Lymphatic structures are their normal habitats. Finally, we have seen that Reuter found fat droplets "in the lymphatic corpuscles of the diffuse lymphoid tissue." Launois likewise found fat in many of the supposed true epithelial cells of the pituitary, as shown by staining reactions, osmic acid, etc.

The function of these cells in the anterior pituitary likewise assumes a normal aspect, since it is essential that broken-down cells, including the leucocytes which have secreted their products into the organ, should be promptly eliminated. This is essentially the rôle of the mononuclears, acting as Metchnikoff's macrophages, *even when epithelioid, i.e.,* when forming part of an epithelium from which they can free themselves and migrate away. Thus, as stated by Ziegler,[31d] "proliferating tissue can produce cells which appear very like the larger forms of mononuclear leucocytes." Hektoen,[31e] on the other hand, states that "in typhoid fever a marked proliferation occurs in the endothelial cells of the lymph-follicles of the intestine, mesenteric lymph-nodes and spleen; and the new cells acquire marked phagocytic properties." Or, instead of migrating from the organ, these mononuclears may combine to form a giant cell. Referring to the formation of tubercle, for instance, Metchnikoff[317] writes: "It is composed of a collection of phagocytes" . . . . . "which move towards the spot where the bacilli are situated and englobe them. The phagocytes retain their condition of epithelioid cells, or are transformed into giant cells." All this illustrates mononuclears in the act of apprehending pathogenic elements, detritus, broken-down cells, etc., of some kind, though forming part of the organ's parenchyma, and applies as well to the anterior pituitary as to any other lymphatic organ. Interpreted from my standpoint, therefore, *what is now regarded as the glandular epithelium of the anterior pituitary is mainly composed of promiscuously distributed epithelioid mononuclear macrophages, which carry on therein, as elsewhere, their function of general scavengers.*

[31c] Böhm, Davidoff and Huber: "T. B. of Histol.," p. 197, 1905.
[31d] Ziegler: "General Pathology," p. [illegible], 1896.
[31e] Hektoen: "Amer. Text-book of Pathol.," p. 149, 1901.

Although he does not in any way refer to cells of the anterior pituitary as leucocytes—regarding them, in accord with all other investigators, as true epithelial cells, Launois's description of these elements clearly points to them as leucocytes, including the large mononuclears and giant cells referred to above. Thus, he refers to three types of cells found in the gland, judging, he says, "from their tinctorial affinities," as *"acidophiles," "basophiles"* and *"chromophobes."* Indeed, some cells, he says, recall when stained "the *neutrophile* granulations contained in certain leucocytes." Now, in Figure 1, we saw that "polynuclear" leucocytes are present, while the cells just referred to are "neutrophiles." Moreover, as I have previously shown, these are precisely the nutritional leucocytes which I traced from the intestinal canal to the tissues.

Launois refers also to the "acidophiles" as "siderophiles." We have seen in Gulland's plate opposite page 668 (first volume) that corresponding leucocytes also take the iron-hæmatoxyline stain and are colored black by it. The mitoma or networks present in these cells are also observable in the supposed epithelial cells, for Launois refers to the presence of a "reticulum." The basophiles likewise correspond tinctorially with leucocytes; they stain violet-blue with hæmatoxyline, pink with hæmatin-eosin, orange-yellow with hæmatin-eosin orange—even though there is good reason to believe that as soon as they enter the organ—or rather its anterior lobe—leucocytes promptly secrete their granules and thus lose their main staining affinities. This accounts—only from my viewpoint, of course—for the presence in the organ of the cells to which Launois refers as "chromophobes" (Comte), *i.e.*, cells which have but slight affinity for stains.

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[317] Metchnikoff: "Lectures on the Comparative Pathol. of Inflam.," Starling's transl., 1893.

Regarded as leucocytes, and as I interpret their function, these "chromophobes" are merely depleted leucocytes. Thus, Launois refers to them as "still containing" *very few* "acidophile," "basophile" or "siderophile" granulations. They are found disseminated among the other elements of the organ and aggregate in clumps, the periphery of which is alone stainable. At first the granules accumulate in masses, which Launois connects "intimately" with the secretory process of the organ considered as a gland; interpreted from my standpoint, however, these granules are the identical granulations which leucocytes secrete elsewhere, and that are here used by the organ as a secretion. Indeed, Launois refers repeatedly to the presence of "granulations." In the basophile cells, for instance, he found the protoplasm rich in granulations "which have an elective affinity for basic dyes." In fact, he actually mentions the escape of granulations in the neighboring fluids and their dissolution therein. Scaffidi[33] has likewise observed that the cells of the anterior pituitary shed their granules, and that when this is accomplished, the cytoplasm is disposed closely around the nucleus. Such cells are shown in the plate opposite page 1050.

All this explains why supposed "glandular cells" are so promiscuously distributed in the organ. Thus, Launois states that the distribution of these cells is very irregular, some "cords" being composed of eosinophiles, others of basophiles only, but that in general the different types are met with "in the one cord." At times the cells are distributed equally in all regions of the gland; at others, certain territories are richer in basophiles, others in acidophiles. There is as to this, he remarks, no fixed rule.

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[33] Scaffidi: Arch. f. mikros. Anat., Bd. lxiv, S. 235, 1904.

Briefly, besides the great mononuclears, which are probably evolved *in situ*, since small mononuclears are also present in great numbers, and giant-cells, all of which are described by Launois under the belief that they are true epithelial cells, the organ contains the more familiar blood leucocytes, *i.e.*, neutrophiles, basophiles and acidophiles.

Before the details of the functional mechanism of the anterior pituitary, as interpreted from my standpoint, can be submitted, a few anatomical facts must be reviewed.

The leucocytes, as we have seen, are present not only in the tubules of the organ, but also in its capillaries, which are, according to all classics, very abundant. These are, as shown by Obersteiner,[33] the continuation of a number of vessels which pass from the base of the brain to the anterior lobe along the anterior surface of the infundibulum. Launois traced them to the internal carotid and refers to them as the "intrinsic" vessels of the organ, in contradistinction to its "extrinsic" supply, *i.e.*, two sets of thin vessels, also derived from internal carotid but which are distributed to the surface. The intrinsic veins of the organ also pass upwards along the infundibulum and meeting those derived from the extrinsic veins probably empty, according to Launois, in the deep sylvian vein. Both the intrinsic arteries and veins, according to Berkley,[34] "directly pass" into the anterior lobe "from the substance of the infundibulum." He speaks of a "large number of vessels" in this connection, a fact which accounts for the very rich supply of capillaries throughout the organ and between the tubules, which, as stated by Gray,[35] are united together by a very vascular connective tissue." It is apparent that leucocytes can readily enter the anterior pituitary with its arterial blood, and penetrate to every part of this organ.

That it is possible for the leucocytes to circulate freely in these parenchymatous capillaries and also to migrate through their walls, is shown by the fact that Obersteiner[36] found the vessels which pass between the cellular tubes "numerous and large" and their walls "remarkably thin"—so much so, indeed, that Launois observed actual tears in the capillary walls of overactive organs which afforded a free communication with the tubules. The annexed microphotograph, in which leucocytes are present among many red corpuscles, clearly suggests, in [illegible] that the connective tissue walls of the tubules and capillary walls are one, and that, as elsewhere in the body, leucocytes [illegible] with food-products, drugs, poisons, etc., can readily enter the tubules. Such leucocytes are plainly shown in the tubules in the same illustration. Here they evidently secrete their contents, for, as Comte has suggested, and as Launois was able to show by staining methods (although of course unaware that he was dealing with leucocytes), "two secretory products, one *basophile* and the other *acidophile,*" are secreted, while the "intermixture of the cells which elaborate them indicates that these two products are themselves mixed before being eliminated from the parenchyma."

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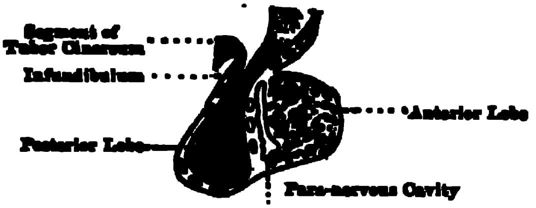
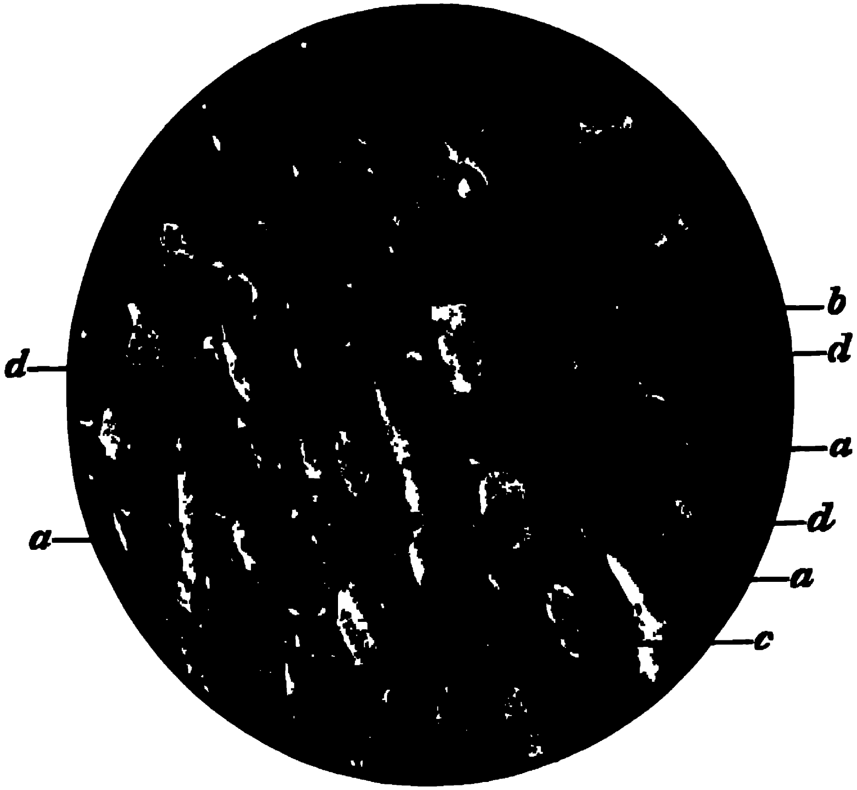
[33] Obersteiner: Soury, "Système nerveux central," vol. ii, p. 784, 1899.
[34] Berkley: Brain, Winter, p. 517, 1894.
[35] Gray: "Anatomy," p. 664, 1901.
[36] Obersteiner: *Loc. cit.*



PERPENDICULAR ANTERO-POSTERIOR SECTION OF THE PITUITARY BODY OF A HUMAN EMBRYO OF FOUR MONTHS. (*Edinger.*)

Interpreted from my standpoint these are all very important features of the question in point. The leucocytes, containing as they do whatever they may have absorbed in the intestinal canal or in the blood, are distributed, we have seen, throughout the entire organism. What proportion of these cells happens to penetrate into the pituitary to form the supposed secretion is, as it were, a *sample of the food-elements and any noxious substance that they may contain, which are being distributed broadcast.* The blood as the bearer of leucocytes thus laden, fulfills the rôle that sea-water does in lower forms.

In these lower organisms, however, we have seen that the "respiratory fluid" and the food materials it contains are brought into contact with the center of their auto-protective mechanism, their "test-organ" or "osphradium." How is the corresponding process carried on in the anterior pituitary of the higher animals, including man?



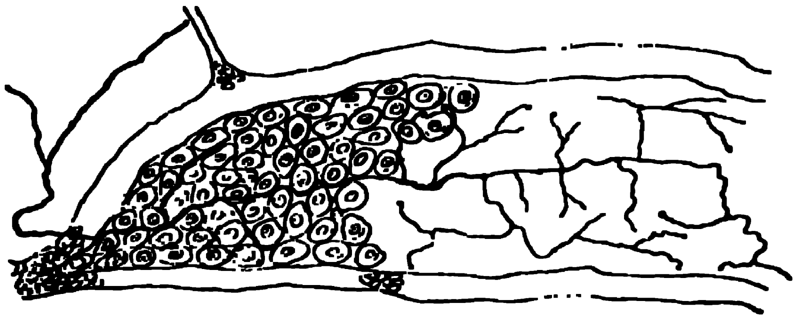
PROMISCUOUS DISTRIBUTION OF CELLS IN THE ANTERIOR PITUITARY. *[Sajous.]*

a, Large epithelioid phagocytes. b, Neutrophile-nutritional-leucocytes. c, Basophile leucocyte. d, Capillaries.

[illegible] cavity, but which in reality is closed [illegible] varies greatly in shape; it may be broken up [illegible] that unite the two surfaces, or form a relatively [illegible]; it may also appear closed, the two walls being [illegible] contact even though their cellular elements are different [illegible]. Thus while the surface forming part of the anterior lobe is lined with ciliated epithelium, that of the par-[illegible] proper is composed of the sensory epithelium which, as shown below, forms the test-organ. Now, this cavity doubtless fulfills some important function: "The cavity proper of the para-nervous slit, the capacity of which varies," writes Launois, "contains a peculiar substance, the quantity of which is itself subject to the greatest fluctuations. This substance, which is apparently elaborated by the epithelial elements of the walls, is a mixture of *acidophile, amphophile* and mucoid secretion. While it recalls the materials we found in the parenchyma of the pituitary, it differs from it in being more *granular*, less homogeneous, and less compact. Staining methods show, moreover, that this substance is subject to currents, whirlpools and localized accumulations". . . . "and afford a new proof of the diversity of secretions of which the pituitary may be the source."

In the light of my views, these substances are not glandular secretions, which, as we have seen, do not exist, but waves of a colloid compound of dissolved granules derived from food-products, normal or toxic physiological wastes, drugs, poisons, toxins, etc., that the leucocytes have brought to the sponge-like parenchyma of the organ and which the latter—probably owing to rhythmic contractions of its capsules—projects towards the "para-nervous" cavity.

That the anterior lobe is a contractile organ is suggested by the structure of its capsule, the currents and whirlpools, and by [illegible] that delicate nerve-fibers are distributed throughout [illegible]—doubtless the terminals which Ramon y Cajal [illegible] nucleus in the third ventricle. [illegible] describes these fibers as "bundles of small nerves following the course of the arteries" and from which "come off, at irregular intervals, single fibers, or branches from the main stems, which pursue a very irregular course through the glandular substance, crossing over or accompanying the large venous channels in the septa, and finally being distributed upon the coils of the epithelial cells forming the follicles." His drawing of a set of these fibers, including their ball-shaped terminals, is reproduced below. These ball-shaped endings recall strikingly the sensitive terminals found elsewhere in the œsophagus, larynx, bladder, etc. If they are sensory, their purpose suggests itself: to provoke reflex dilatation of the blood-vessels through which the organ relieves itself of the blood which has caused it to dilate. The capsule of the anterior pituitary, containing as it does "a fine network of elastic fibrils" (Launois), dilates when the organ is hyperæmic—as shown by the enlarged appearance often witnessed during hyperactivity such as that observed in eclampsia (Launois and Mulon), the early stages of acromegaly, etc., and contracts again when the venous and lymphatic channels are widely opened. The "currents and whirlpools," etc., observed by Launois in the para-nervous cavity clearly suggest that some such propulsive mechanism must exist in the organ, the semi-fluid substance being no longer within the capillaries and, therefore, under the influence of the *vis a tergo* motion of the blood. The colloid substance being derived from the tubules, the compression necessary to drive it out through the meshes of their connective tissue (see the homologue of such a network in the plate opposite page



SECTION OF ANTERIOR PITUITARY, SHOWING BALL-SHAPED NERVE TERMINALS AMONG CELLULAR ELEMENTS. (*Berkley.*)

1068) must begin in the periphery of the organ—a function for which the elastic capsule is eminently fitted. On the other hand, the pillow of venous blood which separates the pituitary from its pedestal, the sella turcica, affords ample leeway for its preliminary dilatation.

The para-nervous cavity is probably itself distensible, a fact which would account for the variations in shape, the approximation of its walls or "the widened and somewhat globular" outline observed by Launois. Dilatation owing to the accumulation of leucocytic products swept into it when the anterior pituitary contracts, at one time, and contraction when it is emptied at another, affords a logical explanation of the post-mortem appearances witnessed.

The manner in which the blood deprived of the leucocytes that have migrated into the tubules passes out of the anterior lobe is made clear by the fact that it remains in the sinusoidal capillaries. It is therefore returned to the circulation by the venules which terminate in the large veins in the infundibulum.

As to the detritus, scavenger cells, etc., they have a path of their own—one common, as regards the corresponding process, to all lymphatic structures. Müller,[38] in the course of a comprehensive study of the pituitary body from Myxine to man, found that the partition between the two lobes was supplied with a rich network of lymphatics through which glandular products found their way to the general lymphatic system. Lymphatic vessels seem to be absent elsewhere in the anterior pituitary. The process of elimination during life must be a very active one. The microphotograph facing the next page shows a large number of cells in the act of being ejected from the organ (the effect of periodical contractions such as those of the spleen) in a current of "colloid"—an aggregate of lymph, adrenoxidase, dissolved granules, etc., as previously stated. Here as in several slides studied, the mass occurred in what corresponds with the external orifice of the lymphatic spaces, while in other slides the cells had not as yet reached the outlet when death of the organism of which it formed part took place, arresting the progress of the cells to the external lymphatic vessels.

Summarizing all these facts, it seems evident (1) *that the*

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[38] Müller: Jenaische Zeitsch., Bd. vi, 1873; cited by Guépin: Tribune médicale, Dec. 10, 1891.

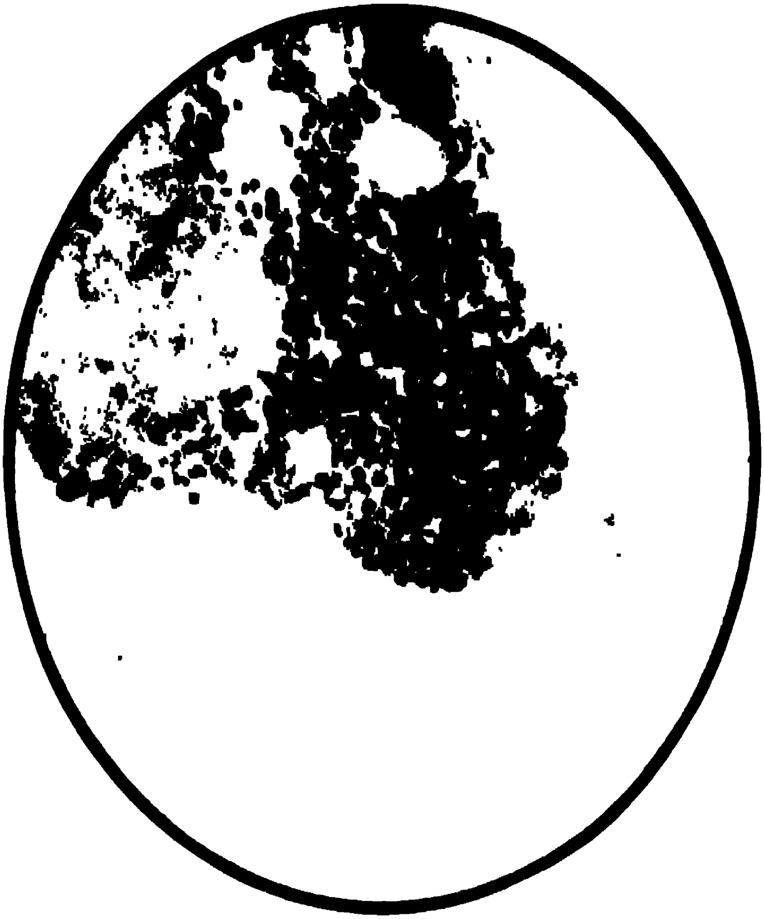
[illegible]

[illegible] in the organ an irregular epithelium; (3) that the [illegible] phagocytic leucocytes, especially the neutrophiles, [illegible] (as they do elsewhere in the body) their granulations and [illegible] products of food-materials, waste-products, drugs, poisons, toxins, etc., ingested by them anywhere in the body, their leucocytes which have been killed by microbes, poisons, etc., are removed as detritus from the anterior pituitary by its mononuclear macrophages; and (4) that this process of elimination is assisted by periodical contractions of the organ such as those of the spleen, which project all living leucocytes and a current of colloid—an aggregate of lymph, adrenoxidase, dissolved granulations, drugs, wastes, poisons, etc.,—into the lymphatic spaces of the organ and then into the lymphatic system, whence they pass into the blood to be destroyed.

The cardinal feature of all this evidence, however, is that the contents of the leucocytes which penetrate into the tubules, *i.e.*, their nutrient granules—more or less dissolved—and any noxious substance that may be harmful to the organism at large, are brought—more or less modified probably by the ciliated epithelium of the anterior wall of the para-nervous cavity—*into contact with the sensitive epithelium, i.e., the test-organ.*

The identity of this organ as a sensitive structure asserts itself from various directions. Gentès, who described this structure in the higher animals, does not refer to the possibility of its being the homologue of the test-organ of ancestral forms. This adds value to his description of the developed organ—to which I attribute such important functions. [illegible] while he describes its superficial layer in the higher [illegible] as composed of "stratified cylindrical epithelium [illegible] certain sensory epithelia," Ray Lankester [illegible] corresponding organ in ancestral animals—as to [illegible] relations—as "a patch of epithelium [illegible] modified and supplied with a nerve [illegible] the point is the [illegible] of [illegible]

[illegible]



LEUCOCYTES WHICH HAVE SHED THEIR GRANULES, LYMPHOCYTES, ETC., IN THE ACT OF BEING EJECTED FROM THE ANTERIOR PITUITARY. (Sajous.)

[illegible] ganglia are [illegible] with a patch of [illegible] epithelium [illegible] siphon, they are sometimes regarded

[illegible] developed condition, however, *i.e.*, in the adult [illegible], rat, guinea-pig, sheep, porcupine, etc., in which [illegible] the organ, it is no longer limited to a mere [illegible] epithelium, but has become a structure occupying a [illegible] portion of the partition between the two lobes. On the side exposed to the "para-neural" cavity are five or six layers of cylindrical epithelial cells which give the surface a bosselated appearance, and "recall exactly," says Gentès, "the sustentacular element of *the olfactory* mucous membrane." These cells were found to send numerous fibers to the deeper elements and to connect with "foot-shaped" cells which, in turn, were the source of many fibers distributed very freely throughout the structure. Underlying the cell bodies of the epithelial cells, were two or three rows of bipolar cells which sent fibers towards the surface and also to the deepest layers. A third set of fibers was found to arise in the midst of all these elements and to pass posteriorly through the partition and thence into the maze of cells and fibers which form the neural lobe. These fibers, we have seen, were finally traced by Gentès some distance in the organ and thence by way of the infundibulum to the tuber cinereum.

May not these fibers have come into contact in the neural lobe with other cellular elements? In that case, there would be complete correspondence between the olfactory organ of the pituitary with that of the nasal cavities, including its cerebral segment of the olfactory bulb. Indeed, while Gentès emphasizes the striking resemblance of the sensitive epithelium of the structure described by him to the sustentacular cells of the olfactory region—which are superficial sensory elements—Berkley,[illegible] ten years before, alluding to certain cells in the posterior [illegible]: "Very much more strongly do they resemble the [illegible] of the *mitral* cells of the olfactory bulbs." The fibers [illegible] would, under these conditions, be the functional homologues of the olfactory nerves.

[illegible] *Loc. cit.*

Whether this connection exists or not, the fact remains that the sensitive organ—the test-organ—sends nerves to the tuber cinereum, where they connect, as I have shown in the previous section, with a nerve-chain which terminates in the adrenals, the secretion of which, as will be shown presently, is the fundamental factor of the body's auto-protective or immunizing functions.

The main function now attributed to the anterior pituitary body by all authors—that of a secreting organ—finds no place in my interpretation of its rôle in the organism. That it has ceased to secrete when fully developed, *i.e.*, in the higher animals, is shown by various facts:—

The thyroid gland and the adrenals, which are positively known to be the source of a secretion, produce extracts which are very active. Such is not the case, however, with extracts obtained from the anterior pituitary. Howell[41] found that such extracts "when injected intravenously have little or no physiological effect." Garnier and Thaon[42] recently confirmed Howell's observation with extracts prepared from the anterior pituitary of oxen. This is accounted for by the fact that, as I interpret the phylogenetic history of the organ, it ceases to secrete when the adrenals appear.

In the diagram of a sea-squirt shown herewith—a longitudinal section of the animal—the pituitary body (*hyp*) may be seen to send a projection to the respiratory apparatus (*stig*) *i.e*, the duct of the pituitary. The purpose of this relationship is not known. In my opinion this secretion penetrates into the cellular elements composing the respiratory organ, and *endows its blood with the property of absorbing oxygen,* while the water is driven through the stigmata by the active movements of their ciliated epithelium. Indeed, we have seen that in the experiments of Piéri and Portier and others, including my own, in the clam, oyster, and sea-mussel, the (colorless) blood of the gills gave the guaiac-test most actively, thus showing that it was rich in oxidase—the substance which in animals supplied with adrenals I have termed "adrenoxidase." As shown by Abelous and Biarnès, this same active reaction was obtained from the corresponding blood in crayfish, by Phisalix in batrachians, and so on until the highest mammals were reached—always with blood derived from the respiratory organs.

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[41] Howell: "Text-book of Physiology," p. 778, 1905.
[42] Garnier and Thaon: Jour. de physiol. et path. génér., Mar., 1906.

This interpretation is further sustained by the evident connection between the "subneural gland"—the primitive anterior pituitary—and the respiratory organs of another ascidian in which the duct is very long, *Phallusia mentula*. Willey,[48] referring to the structure in which the duct terminates, describes it as the "dorsal tubercle, the opening of the hypophysis into the *branchial* sac." Briefly, in the light of my work, in these invertebrates the ancestral anterior pituitary fulfills the functions which in the higher animals are carried on by the adrenals.

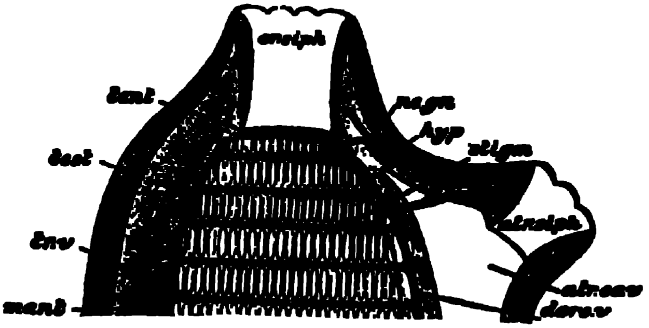

DIAGRAM OF THE UPPER SEGMENT OF A SEA-SQUIRT, ILLUSTRATING THE CONNECTION BETWEEN THE PITUITARY BODY (*hyp*) AND THE ANIMAL'S RESPIRATORY APPARATUS (*stigm*).

ne. gn., nerve-ganglion or general nerve-center; *or. siph.*, oral siphon; *atr. siph.*, atrial siphon; *tent.*, tentacles; *test*, bag; *mant.*, mantle; *tr. v.*, transverse vessel; *dors. v.*, dorsal vessel; *atr. cav.*, atrial cavity. (*Parker and Haswell.*)

When does the transition take place? This question cannot be answered with any degree of accuracy in the light of available knowledge. The adrenals are now thought to occur in the vertebrates only. A study of the question has led me to believe, however, that they appear much earlier, and that in many invertebrates organs which are now regarded as nephridia—and which as such occupy anomalous positions in their relations to the heart and other organs—are naught else, functionally, than adrenals. This question cannot of course be treated in the present work.

Remaining in this connection within the precincts of accepted views based on the embryology, phylogeny and comparative morphology of the subject, we may conclude with Launois that "from Tunicata to man, there occurs, in all species of animals, towards *the base of the encephalon an organ formed by the intimate contact of* a nervous projection with a projection of the stomodæum. In all except Myxine, doomed to retrogression owing to its parasitic life, the stomodæal projection becomes glandular. The gland thus formed is tubular and rich in blood-vessels. While it opens externally in Tunicata and Amphioxus, it *becomes a closed gland* from the earliest of vertebrates." Hence the prevailing belief that it supplies the blood an internal secretion. Not only, however, has the rôle of this supposed secretion in the organism never been found, but, as we have seen, the organ contains no active substance, while the promiscuous distribution of its cells, the character of the latter, and other facts, indicate that the anterior pituitary is not a secreting gland.

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[48] Willey: "Amphioxus and the Ancestry of Vertebrates," p. 190, 1894.

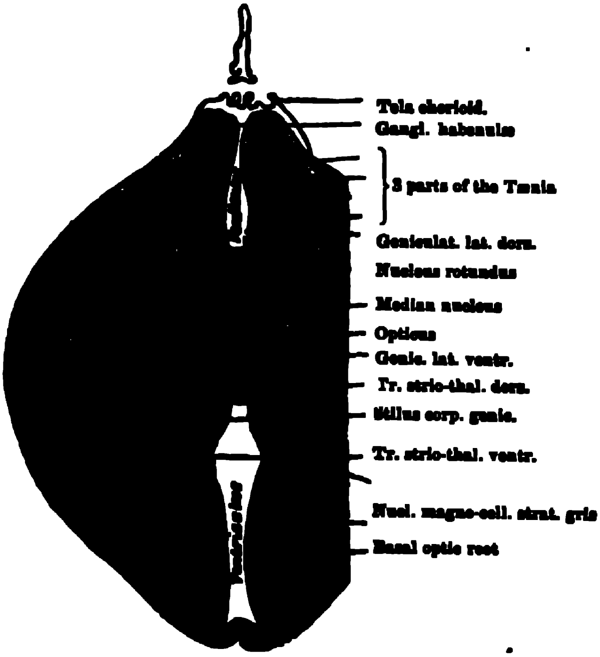

FIG. 1.

VERTICAL SECTION THROUGH THALAMUS OF A YOUNG ALLIGATOR, SHOWING THE GREAT-CELL (NUCL. MAGNO-CELL. STRAT. GRIS.) NUCLEUS OF GRAY MATTER. (*Edinger.*)

With the evident connection between the anterior pituitary and the respiratory organs of ancestral animals I have indicated, the obliteration of the external opening in the early vertebrates assumes a normal aspect in that it coincides with the appearance of the classical adrenals. Indeed, these organs are not only present in the higher mammals, but also in amphibians and fishes, including those classed among the lowest Chordata, the Elasmobranchii (shark, dog-fish and ray). In these animals, moreover, a suggestive feature asserts itself, viz., the presence in the floor of the third ventricle of the nervous structure through which, as I have shown, the pituitary body is united with the upper portion of the spinal system. "One finds in birds and reptiles, probably also in fishes, in the midst of the gray matter that surrounds the median ventricle," writes Edinger,[44] "an elongated nucleus of large cells: *Nuc. magno-cellularis strati grisei.* It is probably fibers from it that pass ventrally to cross just over the infundibulum as the *Decussatio supra-infundibularis.* Besides this, it probably sends bundles off posteriorly." In the annexed illustrations, Fig. 1 indicates the great-cell nucleus, divided vertically, while Fig. 2 shows

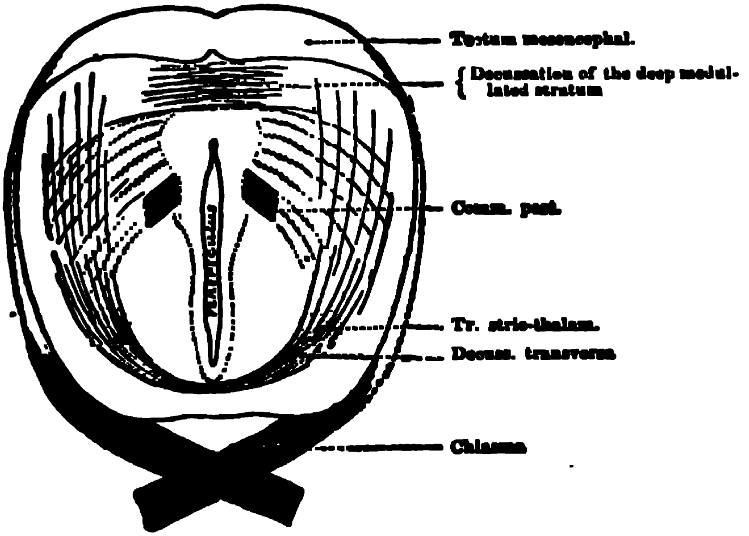

FIG. 2.

HORIZONTAL SECTION THROUGH BASE OF BRAIN OF A SHARK, SHOWING FIBERS FROM GREAT-CELL NUCLEUS. (*Edinger.*)

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[44] Edinger: "Anat. of the Central Nervous System," p. 132, 1899.

fibers derived from it proceeding posteriorly—the path which, as shown in the preceding section, leads to the adrenals.

The evidence submitted in this section appears to me to warrant the following conclusions: (1) *The anterior lobe of the pituitary is not, as now believed, a secreting gland, nor the source of an internal secretion;* (2) *it fulfills in all higher animals, the same function that the osphradium or test-organ does in various invertebrates and lower vertebrates, viz., it tests the purity of the respiratory and nutritional fluids, i.e., the blood in the higher vertebrates; including man;* (3) *inasmuch as, in these higher vertebrates, the food-products, normal and toxic wastes, drugs, and poisons are taken up by leucocytes in the alimentary canal and the blood, and distributed by them to all parts of the body, the anterior pituitary, a highly vascular organ, receives its share;* (4) *while the plasma and red corpuscles remain within the vessels of the anterior pituitary, the leucocytes migrate through the walls of its capillaries and accumulate promiscuously in the anastomosing tubules of which the parenchyma of the organ is composed;* (5) *once in these tubules, the leucocytes secrete their granulations, acidophile, basophile and amphophile, and any other substance, benign or toxic, they may contain;* (6) *all these substances dissolve in the tubules, in fluids derived from the leucocytes themselves, and (as will be shown) adrenoxidase derived from the red corpuscles in the capillaries;* (7) *a colloid substance is thus formed which contains a given proportion of all the benign and toxic substances that are being distributed to the body at large;* (8) *this colloid substance represents, therefore, a specimen of the nutritive materials which the tissue cells are assimilating;* (9) *this specimen enables the test-organ of the anterior pituitary to take cognizance of any noxious substance or drug that may be contaminating these nutritive materials.* (10) *The test-organ of the higher vertebrates, including man, is located in the superficial tissues of the partition separating the anterior from the posterior pituitary, and faces the parenchyma of the former;* (11) *the elastic capsule of the anterior pituitary contracts periodically, each contraction causing compression of its sponge-like parenchyma and propulsion of its colloid substance posteriorly, i.e., towards the test-organ;* (12) *the colloid substance is thus projected into a* *cavity between the parenchyma and the test-organ and brought into contact with the latter on its way out of the pituitary through lymphatics;* (13) *the test-organ is a sensitive structure the surface of which—that exposed to the colloid substance—is similar to that of the olfactory membrane;* (14) *it sends fibers into the posterior lobe of the pituitary, which fibers* ultimately pass upward to the tuber cinereum, where they merge with the nerve-chain that terminates in the adrenals—the organs which, when stimulated by the test-organ, awaken a protective reaction in the body at large.*

LEUCOCYTES AS THE PURVEYORS OF THE THYROID AND PARATHYROIDS, AND AS THE SECRETING CELLS OF THESE ORGANS.

A Swedish anatomist, Sandström,[45] discovered in 1880, in man and various other mammals, small epithelial organs near to, or forming part of, the thyroid gland, *i.e.*, the parathyroids. Thanks mainly to the investigations of Gley,[46] who first showed their great physiological importance, Moussu,[47] and Vassale and Generali,[48] whose observations have been confirmed by many other investigators, these small organs have been shown to influence greatly the vital functions. The difference between them and the thyroid in this respect is quite evident, however: as stated by Jeandelize,[49] "to the thyroid belongs a trophic function of the first order, its removal being followed by disorders of nutrition, while, conversely, extirpation of the parathyroids is followed by convulsive phenomena."

Notwithstanding the considerable labor bestowed upon the thyroid and parathyroids, the nature of the relationship between them has remained obscure. Thus Howell,[50] in his textbook of physiology concludes that "the functional connection between these two organs is as yet quite unexplained." This applies as well to the physiological purpose of the parathyroids. H. Richardson,[51] for instance, in his work on the thyroid and parathyroid, writes: "Of the function of the parathyroids little is known at present; they appear to be connected with the thyroid and perhaps to have some special relation to the nervous system." The facts submitted in the two preceding sections appear to me to elucidate several features of the problem.

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* Further histological researches will doubtless show that the fibers of the test-organ do not themselves ascend to the tuber cinereum, and that they terminate in the posterior pituitary, but in functional contact with the cell-bodies of motor neurons, whose neuraxons would then become the initial fibers of the pituitoro-adrenal nerve-chain.—S.

[45] Sandström: Upsala Läkareförenings Förhandlingar, Bd. xv, S. 441, 1879-1880.

[46] Gley: C. r. de la Soc. de biol., p. 843, 1891.

[47] Moussu: Thèse de Paris, 1896-97.

[48] Vassale and Generali: Arch. ital. de Biol., vol. xxxiii, p. 23, 1900.

[49] Jeandelize: "Insuffisance thyroïdienne et parathyroïdienne," p. 3, 1902.

[50] Howell: *Loc. cit.*, p. 774.

D. A. Welsh,[52] after an elaborate anatomical and experimental research upon the parathyroid glands, concludes: "The anterior lobe of the pituitary body bears a close resemblance in some of its structural features to the parathyroid glands: (1) In both there occur two kinds of cells, the one characterized by a homogeneous diffusely staining protoplasm and a relatively large pale nucleus, the other by a relatively small dark nucleus and an oxyphile granulation of its protoplasm. (2) In both there may occur acini whose lumina may be occupied by small lobules of colloid substance, or, more sparsely, larger spaces containing larger masses of colloid."

The resemblance to the anterior pituitary asserts itself even more strongly when various facts recorded by Welsh are compared with some quoted from Launois's work—that reviewed in the preceding section. Thus, we have seen that the parenchyma of the anterior pituitary was composed of leucocytes distributed promiscuously, and of anastomosing tubules separated by connective tissue partitions in which coursed the capillaries, arterial and venous. Welsh, in describing the parenchyma of the parathyroids, refers to a type in which "the cells tend to be arranged in continuous anastomosing columns, between which connective tissue septa and capillary channels are found." Of another type he says: "The irregular cells occur irregularly scattered among the principal cells, either singly or in groups of three or four, without definite arrangement." These cells, as he also states, have "a very characteristic and constant structure" while their protoplasm "shows a distinct fine granulation. The granules are highly *oxyphile* and readily take up *eosin* and other dyes." He says, moreover, that

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[51] Richardson: "The Thyroid and Parathyroid Glands," p. 72, 1905.
[52] D. A. Welsh: Jour. of Anat. and Physiol., Apr., 1898.

"they show a striking resemblance to the granules of the erythrophile cells of the pituitary body, which are also eosinophilic."

Occurring in greater number than the oxyphiles is that type of cell which Welsh designates as the "principal" cells. These also "may show considerable variation both in the details of their structure and, more particularly, in their arrangement within the gland." He also found that their protoplasm "stains very variously, being sometimes exceedingly clear and faint, at other times darker, with very fine *basophile granulations*. Differences of staining may occur in cells lying side by side in the same acinus." These facts suggest pointedly that, as is the case with the anterior pituitary, the cellular elements of the parathyroids include leucocytes.

Such a conclusion is further sustained by the fact that the proportion of cells is a fluctuating one. Indeed, as stated by Welsh, "the granular oxyphile cell may not be present at all." If we were dealing with organized epithelial tissues, the elements themselves would not disappear. Again, as stated by Rogers and Ferguson,[53] referring to human parathyroids, "they are small and they rapidly decompose or rather undergo autolysis; hence the ordinary dissecting-room cadaver cannot be utilized for their study." This is readily accounted for when its cells are regarded as leucocytes, for we have seen that leucocytes contain ferments, adrenoxidase, etc., *i.e.*, various digestive triads. Again, such a structure—a delicate spongy framework in which the parenchyma of a true secreting organ is replaced by blood-fluids, colloid material and flowing, amœboid cells—should be readily compressible and easily influenced by blood tides. In describing the parathyroids, MacCallum[54] writes: "In color they are of a clear light brown, which may be rendered pale by anæmia and the accumulation of fat, or converted into a brownish-red by congestion. It is particularly this light brown color, together with their flabby softness, which makes them easily recognizable."

This evidence only permits of one conclusion, however, viz., that *leucocytes penetrate into the parathyroids, and secrete their granulations therein.*

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[53] Rogers and Ferguson: Amer. Jour. Med. Sci., May, 1906.
[54] MacCallum: Brit. Med. Jour., Nov. 10, 1906.

What is the identity of these leucocytes? The cells to which Welsh refers as varying greatly in number, and even as absent at times—thus emphasizing their migratory nature—are granular oxyphiles which "readily take up eosin." This happens to coincide with the leucocytes, which take up iodine physiologically.

Iodine is now generally recognized as the main active principle of the parathyroid secretion. Gley found[55] that the relative proportion of iodine was six times greater in the parathyroids than in the thyroid in dogs, and twenty-five times greater in the parathyroids than in the thyroid in rabbits. Pagel[56] also found iodine in the parathyroids. Now iodine is not only taken by eosinophile leucocytes, but these particular cells are found in the alimentary canal and tend to accumulate in certain organs—thus accounting for their accumulation in the parathyroids.

That leucocytes absorb iodine under normal conditions was recently demonstrated by M. Labbé and Lortat-Jacob.[57] Labbé,[58] alluding to this paper, writes: "Immediately after injecting either Gram's solution or iodine dissolved in vaseline into the peritoneum [of various animals], certain leucocytes may be seen to have taken it up, the drug forming a yellow crescent in the periphery of their protoplasm. Soon, this coloration disappears and the yellow crescent is replaced by a 'rocky' (*sic*) formation indicating the modification undergone by the iodine in the interior of the leucocyte. Its presence may be discerned by chemical reagents: a saturated solution of sublimate gives a brown precipitate if the cell contains iodine only, and a mixture of brilliant red and reddish-brown precipitate if an iodo-iodine solution has been absorbed by it. These reactions are no longer obtainable after a certain time, a fact which appears to me to indicate a more complete transformation and assimilation of the iodine by the protoplasm of the cell. With starch the reaction is still more temporary and disappears much more rapidly." The author states, moreover, that when iodine is assimilated and incorporated into the organic molecule, it is no longer possible to detect it, at least by ordinary methods, and that "it is thus found combined as thyroidine in the thyroid." This applies as well to the parathyroids, since we have seen that they also contain iodine.

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[55] Gley: See also Archives de physiol., vol. xxiv, p. 146, 1892: C. r. de la Soc. de biol., p. 843, 1891.

[56] Pagel: Cited by Jeandelize: *Loc. cit.*

[57] M. Labbé and Lortat-Jacob: *Loc. cit.*

[58] Labbé: Presse médicale, Aug. 10, 1904.

The fact that eosinophiles, Welsh's "oxyphiles," are not phagocytes suggests that these cells do not take up iodine. Not only do they absorb it in eosinophilia—though less actively than neutrophiles—but the fact that, in normal animals, the absorption occurs through the surface or periphery of this cell—a process which differs from the "englobing" peculiar to phagocytes—suggests that the eosinophiles must carry on the physiological rôle of taking up this halogen—owing, I may add, to its identity as a specific tissue constituent. Drawn chemotactically to any region in which iodine appears, the alimentary canal, the subcutaneous tissues, the blood, etc., the cells then travel to the organ in which it is either stored or used physiologically. Indeed, while Opie,[59] in a searching analytic study of this leucocyte, states that "large *accumulations*" of them "are not infrequently noted in various organs" . . . . "notably in the mucosa of the *gastro-intestinal* tract, in the mucosa of the air passages, in the lymphatic tissues and in the spleen." Levaditi[60] quotes the observations of Seifert and Leredde that the use of potassium iodide is accompanied by an increase of eosinophiles in the blood. The "digestion leucocytosis" affords a clear example of the process, though in the present connection the oxyphile-eosinophiles play the active rôle when iodine or the iodides are ingested or injected subcutaneously, and transfer them to special tissues, including the parathyroids.

What is the relationship of these cells to the elaboration of the iodine-laden secretion of the parathyroids?

This is met, to a certain extent, by the observation of Labbé that the iodine is transformed chemically *in* the leucocytes—to such a degree, in fact, that after a given time, it forms part of a new molecule and can no longer be detected by tests which do not break down the latter. "These transformations," says this investigator, "occur under the influence of the active *ferments* contained in the body of the leucocytes; the

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[59] Opie: Amer. Jour. Med. Sci., Feb., 1904.

[60] Levaditi: "Le leucocyte et ses granulations," p. 116, 1902.

oxidases, the presence of which was demonstrated by Portier, doubtless play an important rôle in these chemical reactions." This recalls a salient feature emphasized in a preceding chapter: that leucocytes are minute laboratories in which compound substances required by tissue-elements are built up ready for use. That we are dealing in the present connection with a physiological function carried on by certain leucocytes as elsewhere is evident; the specific function here being to elaborate a secretory product now supposed to be formed by glandular elements.

This conclusion would appear to be weakened by the fact that iodine in relatively large quantities may be obtained readily from the parathyroids and, therefore, before it is bound up in the organic molecule. This does not hold, however, in view of the fact that the leucocytes studied by Labbé and Lortat-Jacob were observed *in vitro*. The intracellular transformations noted, therefore, exemplified those which occur *after* the specific leucocytes enter the parathyroids, even though on reaching the organ the iodine is still in a sufficiently free state to be isolated.

It now becomes a question as to the manner in which the eosinophiles dispose of their secretion in the parathyroid.

The anatomical characteristics of a parathyroid correspond very closely with those of the anterior pituitary. It is also divided into tubules by a reticulum. Welsh, for instance, states that "from the deep surface of the capsule fibrous septa may be given off which penetrate the gland and produce an irregular lobule formation." The "lobules" are evidently tubular and contain leucocytes, for Carnot and Delion[61] refer to the presence in tuberculous parathyroids studied by them of a *leucocytosis* "in their epithelial gut-like tubes"—a fitting description of the anastomosing tubules. Their mode of penetration into these cavities—by migrating therein—is evidently the same as in the anterior pituitary, for, according to Minot,[62] "the capillaries between the cell masses . . . . may be regarded as sinusoids"—the typical arterial channels found in the anterior pituitary.

The blood (and its leucocytes) penetrates into the organ also by way of its pedicle and is distributed by a fan-like system of irrigating channels, as is the case in the anterior pituitary. MacCallum describes its supply as made up of a "stalk of minute blood-vessels which spring, in the case of the upper gland (unless it is greatly displaced), from the superior thyroid, while those supplying the lower gland arise from a branch of the inferior thyroid artery." Welsh[63] states, however, that "only one artery, as a rule, enters each parathyroid, usually at its more tapering extremity. It then runs parallel to the long axis of the gland, and, on transverse section, is found to occupy a more or less central position. From the *central artery* lateral branches are given off at frequent intervals along its course. They do not pass off at right angles to it, *but radiate obliquely*, being directed towards the broader extremity of the gland."

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[61] Carnot and Delion: C. r. de la Soc. de biol., Oct. 21, p. 321, 1905.

[62] Minot: Böhm, Davidoff and Huber: "Text-book of Histology," p. 321, 1905.

A parathyroid differs from the anterior pituitary, however, in that its blood is returned, at least in great part, after permeating the organ, by venous sinuses underlying the capsule. Thus Welsh writes: "The venous return is effected in two ways: (1) By venous branches accompanying the arteries and opening into a central channel which runs alongside the central artery and emerges with it. The veins into which these vessels discharge vary according to the position of the parathyroid. Thus they may join the venous branches on the surface of the thyroid. (2) Numerous venous channels lie *immediately underneath the capsule* of the parathyroid, and form the delicate reticulum, which is a character of the naked eye appearance of the gland. Microscopically, they may appear as *dilated, thin-walled sinuses*. They do not seem to have any constant course, but empty into œsophageal, tracheal, or thyroidal veins indifferently."

Interpreted from my standpoint, Welsh's description indicates the itinerary of the eosinophiles in a parathyroid: they enter with the blood of the central artery and are distributed through the intermediary of its radiating branches. They migrate through the walls of these capillaries and into the tubules where we found them.

The nature of the functions of these endogenous cells may be surmised from their behavior in the anterior pituitary:

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[63] Welsh: *Loc. cit.*

they secrete granulations in the tubules and these, dissolved in the plasma (including adrenoxidase, as will be shown) derived from the capillaries, form the secretion of the organ. We will see presently that "a homogeneous granular substance" which gives the reactions of the colloid is present around the vessels.

What is the nature of the second type of cells, those to which Welsh refers as the "principal" cells?

The fact that this author states that "no matter how deeply the cell protoplasm may stain, there is almost never any distinct granularity, and that in the exceptional instances in which it is present, the granules are exceedingly fine and take on only *basic* dyes," suggests, in accord with the prevailing interpretation, that they are simply epithelial cells. Several features lead me, however, to consider them as basophile leucocytes.

The absence of granulations does not militate against this view, since, as we have seen, in the fifteenth chapter, these cells readily secrete these products. The "principal" cells, considered in this light, are merely basophiles which have shed their granulations. Levaditi states, in fact, that "basophile granulations resist but slightly dissolving agents."' Like these leucocytes, the "principal" cells, as stated by Welsh, and also by Kölliker,[64] are supplied with a chromatic network. They vary in size, thus showing transitional phases of development, which does not apply to true epithelium. In the pituitary, "basophile cells" which presented all the stain affinities peculiar to basophile leucocytes, were found by Launois to occur in groups and form a lining for the tubules. Welsh refers to a similar disposal of his principal cells. Another feature which militates against the presence of a true epithelium is that "the granular cells [eosinophiles, which vary greatly in number and may even be absent] occur irregularly scattered *among* the principal cells, either singly or in groups of three or four without definite arrangement."

In the parathyroids, basophiles likewise penetrate into the tubules, for, as stated by Welsh, they form in certain areas "isolated masses" surrounded by a fine "fibrillar stroma" in which course "delicate capillaries" or "processes of dense fibrous tissues carrying large vessels." They are evidently the source of a secretion, for here and there they are clearly "grouped in a single layer around a small circular lumen" containing a "colloid substance." The eosinophile cells are also stated by Welsh to form "definite acini, the lumen being occupied by a mass of colloid material." These are not true acini, however. As Petersen[65] says, the colloid "presses the cells into duct-shaped structures."

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[64] Kölliker: "Handb. d. Gewebelehre d. Mensch.," Bd. III, H. 1, S. 325, 1899.

On the whole, it becomes apparent that, judging even from the meager histological work available, the parathyroids owe their secretory activity to the presence of two varieties of leucocytes which are known to secrete their products. That iodine-laden eosinophilic granulations should combine, when dissolved in the plasma, with the phosphorus-laden nucleo-proteid granulations secreted by the phosphorus-laden basophiles, and with the adrenoxidase of the plasma found in the parathyroidal tubules, is not only suggested by the facts submitted, but also, as I will show in another section, by the actual presence of these substances in the parathyroid secretion.

How is this secretion eliminated?

The oxyphiles and basophiles are mixed in certain parts of the organ, but on the whole those of the one variety tend to form closely packed groups, large areas appearing to be composed of only one kind of cell. This is apt to be the case near the capsule, *i.e.*, in close proximity to the sinuses the latter contains. As these sinuses are channels for venous blood, they can hardly serve for the elimination of the secretion. It appears more likely that the colloid substance passes into perivascular lymphatics and through these to what Benjamins has termed the "parathyroid ducts." In the ox, Welsh found "a duct-like structure" containing apparently several channels. Benjamins,[66] as had Kohn in 1885, also found passages to which he gave the above name. "The only histological indication of a duct in man" observed by Welsh "was met in sections of a large parathyroid, in which a few large *spaces* were found lying just outside the gland tissue. These spaces were lined by cubical epithelium, and were filled with colloid matter of different degrees of density." As this refers to the pedicle of the organ, the duct or ducts accompanied the vessels. Welsh's observation harmonizes with that of Capobianco and Mazziotto,[67] who found that the blood-vessels were surrounded by spaces that contained a homogeneous granular substance which gave the reactions of the colloid substance—the secretion. This fact [also urged by Biedl,[67a]] suggests the identity of the channels which the secretions ultimately reach, for the description of the Italian investigators corresponds with that of perivascular lymphatics.

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[65] Petersen: Virchow's Archiv, Bd. 174, Nu. 3, S. 412, 1903.
[66] Benjamins: Ziegler's Beiträge z. path. Anat., Bd. xxxi, S. 143, 1902.

The close functional relationship between the parathyroids and the thyroid, and the fact that the former or their pedicle are sometimes embedded in the parenchyma of the latter—as I have observed in the ox, and as is often the case in the rat (Christiani) and common enough in the dog (MacCallum)—suggest that the secretion of the smaller organs is voided into the larger. In truth, as stated by MacCallum,[68] "it is rare to find them [the parathyroids] very intimately connected with the thyroid." As shown in the annexed diagrams, they are connected with vessels posterior to the latter. "Various irregular combinations of these relations occur," says MacCallum, "and sometimes one or other of the glands is found quite widely separated from the thyroid." In the illustrations annexed to Welsh's paper, some instances are shown in which they lie on the trachea considerably below the thyroid. Rogers and Ferguson[69] refer to an instance in which "a parathyroid gland was found on the middle of the posterior surface of the pharynx at the level of the lower border of the cricoid cartilage, being far distant from the nearest margin of the thyroid gland." In Fig. 6 of the annexed illustration, although complete atrophy of one lobe of the thyroid had occurred, the parathyroid of the corresponding side is nevertheless present. The perivascular lymphatic networks afford a ready means for the transfer of the parathyroid secretion to larger lymphatics of the neck and through these to the subclavian veins, and finally by the superior vena cava to the heart, where it becomes mixed with the venous blood from the entire organism.

The *thyroid* is in many respects a counterpart of the parathyroids, as may be shown by a few salient facts. The struc-

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[67] Capobianco and Mazziotto: Giorn. Int. de Scienze, Nos. 8, 9, 10, 1899.
[67a] Biedl: "Internal Secretory Organs," p. 28, 1912.
[68] MacCallum: Brit. Med. Jour., Nov. 10, 1906.
[69] Rogers and Ferguson: *Loc. cit.*

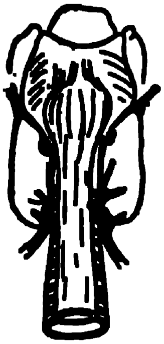

Fig. 1.—Organs of neck from behind. Four parathyroids in their most usual position.

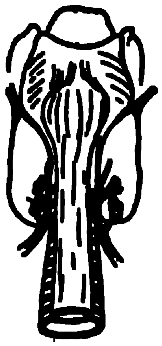

Fig. 2.—The two upper parathyroid glands lie close to the lower pair, which are in their usual position.

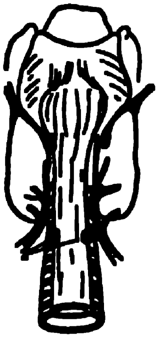

Fig. 3.—The left upper and right lower glands are in their most typical position. The right upper gland lies in the region of the inferior thyroid artery, the left lower gland, supplied by a long arterial branch, is embedded in the posterior surface of the thyroid near its outer margin.

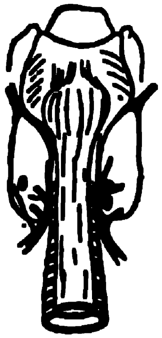

Fig. 4.—The two upper parathyroids are in the common position. The two lower glands lie on the anterior surface of the trachea.

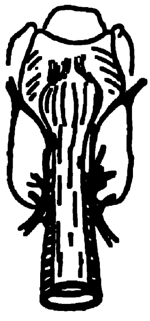

Fig. 5.—Two parathyroids exist on the left side. On the right only one large gland is to be found.

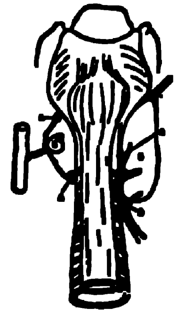

Fig. 6.—On the right side the condition is practically normal; on the left the thyroid lobe is almost completely atrophied, but the parathyroids are found in about the usual situation.

ANATOMICAL RELATIONS OF THE PARATHYROIDS. (*MacCallum.*)

ture of its framework has likewise been carefully studied by J. Marshall Flint.[70] "Almost the entire organ," says this anatomist, "is made up of follicles, the form and relations of which are retained by the connective tissue which embraces them" . . . . "small arterioles, venules and capillaries can be made out in the interfollicular framework or on the membranes which embrace the follicles" . . . . "at times fine bundles run across the basement membranes. These, in some places, form the walls of the capillaries." That such a structure is well adapted for the transmigration of leucocytes, as I have suggested, is well shown in Fig. 1 of the annexed plate, which represents the framework after its contents have been eliminated by Flint's digestive method. He also writes: "By many it has been supposed that the follicles enlarge until they rupture like the Graafian follicles of the ovary, and that their contents are then carried to the systemic circulation through the lymphatics. Others have held that the products of glandular activity passed into the circulation through the membranes by osmosis. At any rate in the specimens of human, dog's and monkey's thyroid where the membranes are distinctly visible, no evidence of rupture is seen in any of them. The meshes are unquestionably large enough for the nourishment and end-products of glandular activity to pass to and from the cells through the reticulated membranes."

The shape of the follicles is likewise that of the tubules in the parathyroids and anterior pituitary. Streiff[71] described them as "ovoid saccules or short-branched tubules with frequent diverticula." He concluded, however, that they did not communicate, and that they were separated by their connective tissue walls. Interpreted from my standpoint, such a structure answers perfectly for the free immigration and emigration of leucocytes. Flint says in this connection: "While the shape of the follicles is, in general, ovoid or spheroid, they are so closely packed together that it is possible to find examples of almost any conceivable form; some are occasionally elongated, some polygonal, others prismatic, and still others almost cylindrical, but the predominating type is distinctly ovoidal or spheroidal."

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[70] J. Marshall Flint: Johns Hopkins Hosp. Bull., Feb., 1903.

[71] Streiff: Cited by Ferguson: "Normal Histology and Microscopical Anatomy," p. [illegible], 1905.

This is well shown in the annexed plate, also from Flint's paper, the walls being those upon which—according to my views—the leucocytes adjust themselves in more or less orderly fashion, to form the so-called "glandular epithelium."

That leucocytes—and other blood constituents—traverse the meshes of the framework is illustrated by the fact that Baber[72] found that the viscid fluid in the follicles—the colloid—often contains blood (and therefore adrenoxidase); and furthermore, that large round cells "migrate into the interior of the gland-vesicles." There are no round cells other than leucocytes in the blood that "migrate;" hence, in accord with what I have shown in the case of the anterior pituitary and the parathyroids, leucocytes evidently enter the follicles. Again, I have pointed out that the walls of the follicles in the organs were formed of rows of leucocytes. Baber terms the migrating cells referred to "parenchymatous cells," owing to their tendency to form part of the glandular parenchyma.

That leucocytes, derived from intestinal canal or the blood, can reach the thyroid as they do the parathyroids, *i.e.*, with the circulating blood, is self-evident. Now, the characteristic stains of eosinophile and basophile granulations are also reproduced in the thyroid: "All follicles which possess any considerable lumen contain a peculiar *acidophile* substance, known as colloid," writes Ferguson,[73] "which is apparently formed by the secretory activity of the glandular epithelium lining the follicles. Colloid is a homogeneous or very finely *granular* substance which stains readily with *eosin*." Again: "Occasionally a single large vacuole, often containing *basophile granules* or crystalloid particles, occupies the centre of the colloid mass in the large follicles."

In the microphotograph from Ferguson's "Histology"[74] reproduced opposite page 1070 (Fig. 2), the leucocytes—the supposed granular epithelium—are not arranged in the beautiful, orderly manner usually depicted by artists in the textbooks: they merely spread out in close proximity to each other promiscuously around the follicles (*a*) and may even accumulate indiscriminately (*b*). This differs widely from the true secreting epithelium, that of the salivary glands, the minute epithelium of the renal convoluted tubules, the intestinal epithelium, etc.

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[72] Baber: Philosoph. Transactions, Pt. III, 1881.
[73] Ferguson: *Loc. cit.*, p. 492.
[74] Ferguson: *Ibid.*

The granules evidently originate from the cells, for Ferguson states that "the cytoplasm of the epithelium is finely granular and decidedly acidophile" and that "minute spheroidal granules which give the color reactions of the colloid are also found in the cytoplasm of the epithelial cells." Finally, he refers to the fact that Hürthle, "by staining with the Biondi-Ehrlich mixture, succeeded in differentiating two types of cells, one lightly staining, the 'chief cells,' the other, a darker colloid-containing type which he designated as 'colloid cells.'" The correspondence with Welsh's parathyroid "principal cells" and the eosinophiles which form acini "occupied by a mass of colloid material" is obvious.

The manner in which the secretion reaches the circulation coincides also with the corresponding process in the pituitary and parathyroids. King long ago traced it to the lymph-vessels. Biondi[75] found that the special secretion of the thyroid in reptiles, apes and other mammalia was produced by the cells lining the follicles and is poured out into the neighboring lymph-spaces. Zielinska[76] showed that although the colloid varied in amount in the thyroids of dogs, the lymph-spaces under the capsule and the parenchymatous lymphatics always contained some. Vassale and de Brazza[77] discovered, around the follicles of the thyroid, a rich network of lymphatics filled with colloid substance from the follicles; and also a similar network in the capsule of the gland. Finally, Zielinska[78] found a colloid substance identical with that in the lymphatics of the gland, in the lymphatic vessels in the neighborhood of the organ. It is evident, therefore, that, as is the case with the parathyroid secretion, it passes to the larger cervical lymphatics; through these to the subclavian veins, and finally by way of the superior vena cava to the heart.

The nerves of the thyroid have alone been carefully studied. Parameschko found that both the arterioles and the parenchyma were supplied with fibers, while Crisafelli showed

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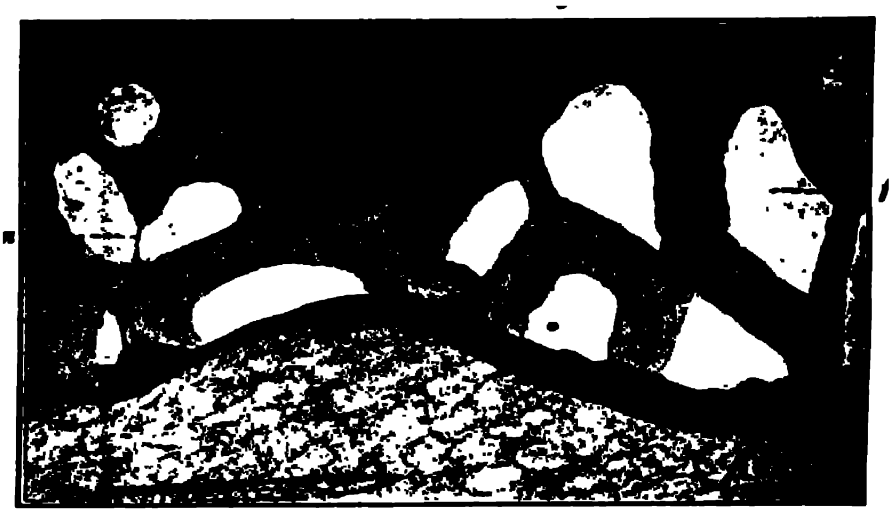
[75] Biondi: Berl. klin. Woch., Bd. xxv, S. 954, 1888.
[76] Zielinska: Virchow's Archiv, Bd. cxxxvi, S. 170, 1894.
[77] Vassale and de Brazza: Arch. ital. de Biologie, T. xxiii, p. 292, 1895.
[78] Zielinska: *Loc. cit.*



SECTION OF DOG'S THYROID 160μ THICK, SHOWING FRAMEWORK OF FOLLICLES, ×100. *[J. Marshall Flint.]*

f, follicles; b, blood-vessels; m, reticulated basement membrane.

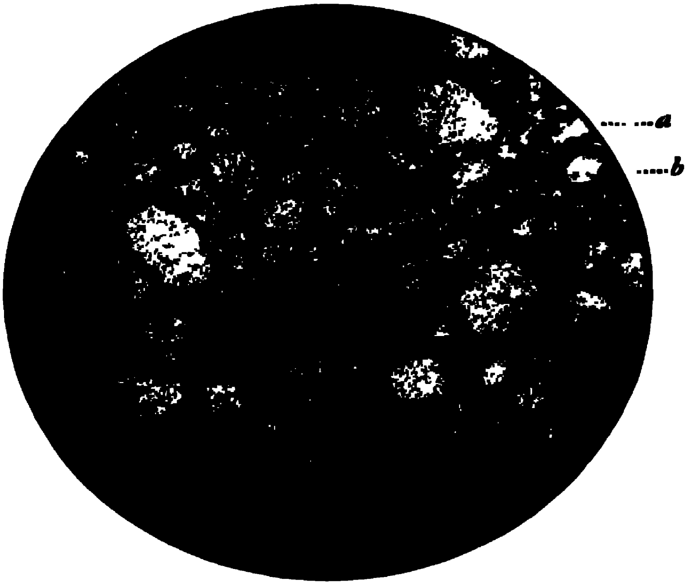


Fig. 2. MICROPHOTOGRAPH OF A SECTION OF THE HUMAN THYROID. *[Ferguson.]*

a, follicles; b, tangential section of follicular wall.

that the vessels were surrounded by plexuses which also involved the parenchyma. Using the Golgi method, Andersson[79] had also noted that they followed the vessels to the latter, but Berkley[80] was first to show their true distribution by the Golgi method, viz., "a meshwork of fibers situated almost immediately *upon the basal surfaces* of the epithelial cells of the follicles." Interpreted from my standpoint, the meaning of this is obvious: the basal membrane facing the interior of the tubules is lined with a meshwork of fibers and it is upon these that the leucocytes lie.

That the thyroid and the parathyroids are morphologically very similar as to the nature of their cellular elements is evident. Another feature asserts itself in the light of the evidence submitted above: the secretions of both sets of organs—the thyroid apparatus as Gley calls them—meet in the superior cava and passing to the heart, must inevitably become thoroughly mixed therein; and then proceed with the venous blood from the organism at large to the pulmonary alveoli, where, as I will show in another section, they are taken up by the *red corpuscles* to be distributed to the body at large—including the anterior pituitary body.

This evidence has served mainly to suggest that both the thyroid and the parathyroids, as well as the anterior pituitary, owe their functional activity to leucocytes and that these cells are their only secretory elements. This means much when the functional relationship between the parathyroids and the thyroid is taken into account, since, as will be shown in the next section, these organs jointly influence the functional activity of the test-organ and through it the secretory activity of the adrenals. The secretion of the latter becoming, when converted into adrenoxidase, the active agent in the vital process, the thyroid and parathyroids supply a link with the vital mechanism on the one hand, and on the other, through the leucocytes, another link with external agencies whether these be introduced through the alimentary canal, the subcutaneous tissues or the veins. From the standpoint of therapeutics and immunity, this fact is of commanding importance, since it places in our hands a lever by means of which we can control the vital activities through the thyroid apparatus and enhance, as we will see presently, the functional efficiency of the processes through which the body protects itself against disease.

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[79] Andersson: Biol. Förening Förhand., Bd. iv, Hft. 5-6, 1891.
[80] Berkley: Johns Hopkins Hosp. Reports, Nos. 4 and 5, p. 112, 1894.

On the whole, the following conclusions appear warranted: (1) *the thyroid and parathyroids are not, as now believed, true glandular organs;* (2) *they are composed of a capsule containing a sponge-like connective-tissue reticulum, the meshes of which form closed tubular cavities lined with a basement membrane, the follicles;* (3) *the follicles are not supplied, as now believed, with a secreting epithelium;* (4) *their secreting cells are leucocytes derived from the alimentary canal or the circulation, which enter the organ with its blood, migrate through the walls of the capillaries in the interfollicular septa and the septa proper, and fix themselves to the follicular basement membrane more or less evenly side by side;* (5) *the granules of these leucocytes are secreted in the follicular fluids and represent the active constituents of the colloidal secretion;* (6) *the secretions of both organs (thyroid and parathyroids) leave them through their lymphatics and ultimately reach the superior vena cava, the heart, and the pulmonary alveoli.*

What is the rôle of the secretion formed by the joint action of the thyroid and parathyroids?

THE ADRENAL SYSTEM (THE THYROID APPARATUS, ANTERIOR PITUITARY AND ADRENALS COMBINED) AS THE AUTO-IMMUNIZING MECHANISM OF THE ORGANISM.

In the first volume, which appeared in January, 1903,[81] I pointed out that the physiological function of the thyroid gland was "to sustain the functional efficiency of the *anterior* pituitary body up to a certain standard, by means of its secretion." Considerable evidence was also submitted, showing that the thyroid secretion, by stimulating the anterior pituitary, sustained the secretory activity of the adrenals, and therefore the activity of the metabolic processes in all tissues; and furthermore, that the three organs thus functionally related—

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[81] *Cf.* also Monthly Cyclo. of Pract. Med., Jan., 1903; Philadelphia Med. Jour., Mar. 7, 1903.

the thyroid, the anterior pituitary and the adrenals—constituted what I termed the "adrenal system."

Although many years have elapsed since I advanced these views, and the organs involved have received greater attention than ever before, my position has not been weakened, while conversely, all solidly established experimental or clinical facts that have come to my notice have only served to demonstrate the strength of the doctrines I have urged.

In the present volume, I have submitted so far considerable additional evidence to the effect: (1) that the adrenal substance on being converted into adrenoxidase, is the oxygenizing agent of the entire organism, and (2) that the anterior pituitary body —its test-organ—governs the functional activity of the adrenals and, therefore, general oxygenation. The third organ of the adrenal system, the thyroid (including the parathyroids, the secretion of which is included in that distributed to the pituitary, and also in the thyroid extracts we use), will now be shown to fulfill the rôle I had originally ascribed to it.

The cardinal rôle of the anterior pituitary body, as the governing center of the adrenals, being to regulate oxygenation, diminution of its functional activity must entail a corresponding reduction of the oxygen supplied to the body at large and, therefore, a reduction of the general temperature. We have seen that removal of the pituitary body or of the adrenals is attended by a steady decline of the temperature, and that this is a characteristic symptom of Addison's disease. On the other hand, I have shown that the anterior pituitary body was the general heat center and that it raised the general temperature by stimulating the adrenals and, therefore, the oxygenation of the body at large. Under these conditions, if, as I hold, the functional activity of the anterior pituitary body is sustained by the secretion of the thyroid gland, overactivity of this organ, or thyroid extract, should cause a rise of temperature, while conversely, removal of the gland or disorders capable of reducing its efficiency as a secreting organ should cause a fall of the temperature. Ample physiological and clinical testimony is available to demonstrate that these conditions are satisfied.

From the standpoint of physiology, Geo. R. Murray,[82] after describing the morbid phenomena that occurred in a rabbit after incomplete removal of the thyroid, refers to the "similarity between the condition developed and that which develops in man and in monkeys after thyroidectomy, as shown by the hebetude, swelling, loss of hair, dryness of skin and low temperature." J. Lorrain Smith[83] observed "a steady fall of body temperature" in every animal (cats), in which he had performed thyroidectomy. Edmunds[84] states that after removal of goiters the temperature is "generally subnormal." In the cat, Jeandelize[85] noted a fall of nearly 3° C. (5.4° F.) though the animal was not then moribund, three days after "parathyroidectomy," meaning thereby the careful removal of the thyroid and parathyroids. In a kitten in which he had left two parathyroids, he also observed "lowering of the temperature," though the post-operative life was prolonged. Referring to experiments by Gley, Rouxeau and Hofmeister in rabbits, in which removal of the thyroid was followed somewhat later by that of the parathyroids, Jeandelize states that "paralysis, hypothermia and chronic phenomena seemed to dominate the scene." Rouxeau[86] in fact states that in his animals "hypothermia was practically constant and often rather accentuated from the start." This applies to all animals, including man.

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[82] G. R. Murray: Brit. Med. Jour., Jan. 25, 1896.

Conversely, the effects of thyroid extract on the temperature are well known. Thus Chantemesse and Marie, and Ballet and Enriquez (Popoff[87]) observed a rise of temperature in animals after the administration of thyroid extract. Similar observations have been recorded by Guéorguiievsky,[88] Bourneville[89] and others. Lewis C. Bruce,[90] having used it in 60 cases, found that it caused fever. In an experimental study Ott[91] was also led to conclude that thyroid produced a rise of temperature, *i.e.*, that it was "a pyrogenic agent." "That thyroid overdosage does quicken the pulse, raise the temperature and cause loss of weight," says F. C. Shattuck,[92] "admits of no doubt." He refers to a case in which, under the influence of excessive doses, the temperature from subnormal rose to 103° F.

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[83] J. Lorrain Smith: Jour. of Physiol., vol. xvi, p. 378, 1894.
[84] Edmunds: Practitioner, April, 1901.
[85] Jeandelize: *Loc. cit.*, p. 45.
[86] Rouxeau: Archives de physiologie, T. xxix, p. 136, 1897.
[87] Popoff: Arch. gén. de méd., Oct., 1899.
[88] Guéorguiievsky: Thèse de St. Petersburg, 1896.
[89] Bourneville: Arch. de neurol., Sept., 1896.
[90] Lewis C. Bruce: Jour. Mental Science, Oct., 1895.
[91] Ott: Medical Bulletin, Oct., 1897.
[92] F. C. Shattuck: Boston Med. and Surg. Jour., June 30, 1904.

Additional evidence from the standpoint of clinical medicine is afforded by the fact that the two diseases now generally ascribed to inadequate activity of the thyroid, myxœdema and cretinism, both present hypothermia as a prominent symptom. Thus while Osler and Norton[93] state that the temperature of cretins is "invariably subnormal" and that "they suffer from cold," Tyson[94] says that in myxœdema "subnormal temperature is characteristic, though in the early stages the temperature may be normal or slightly above. In winter the patient always feels cold and hugs the stove." Lévi and de Rothschild[95] have shown recently, moreover, that aside from these diseases, a large number of disturbances attended with hypothermia, objective and subjective, and often accompanied by vasomotor disorders, cyanosis, neuralgia, chilliness, etc., are in reality due to hypothyroidia and yield to thyroidal treatment. Hertoghe[96] refers to a case in which recurrent chills had suggested the use of quinine in large quantities; then, on the plea that hysteria was present, to the equally fruitless use of the bromides. The chills yielded promptly to thyroid extract, but returned as soon as its use was discontinued.

Suggested in this connection is the fact that the process through which the temperature is raised or depressed by the thyroid apparatus or its extracts has remained obscure, though many tentative theories unsupported by evidence have been vouchsafed. This is a normal result of the fact that, as emphasized by Laulanié (1905),[97] physiologists ("we") "are absolutely ignorant of the mechanism of organic oxidation." With the adrenal secretion as the basis of oxygenation, the test-organ of the anterior pituitary body as the adrenal center, and the secretion of the thyroid apparatus as the physiological stimulus of the test-organ, we have an explanation sustained not only by physiological and clinical evidence, but also, we have seen, by the teachings of comparative zoölogy and physiological botany.

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[93] Osler and Norton: Sajous's "Cyclo. of Pract. Med.," vol. iii, p. 485, 1905.
[94] Tyson: "Practice of Medicine," third edition, p. 678, 1903.
[95] Lévi and de Rothschild: C. r. de la Soc. de biol., Oct. 26, 1906.
[96] Hertoghe: La méd. pratique, Nov., 1906.
[97] Laulanié: "Éléments de physiologie," Paris, 1905.

Again, I have pointed out that, owing to its rôle as the governing center of the adrenals, and, therefore, of general oxygenation, the test-organ of the pituitary governed tissue metabolism. If the thyroid gland sustains, by its secretion, the functional efficiency of this organ, and, through it, oxygenation, it should also influence metabolism. Here again, physiology and clinical medicine harmonize in showing that this influence is very marked.

Removal of the thyroid, we have seen, causes a steady fall of the temperature. This should, if my view that this organ influences oxygenation through the adrenals is sound, reduce the proportion of secretion in the blood and cause a corresponding reduction of its power to take up oxygen. Albertoni and Tizzoni[98] observed that after thyroidectomy "the blood showed less power to fix oxygen." Again, as I have shown that the adrenal secretion formed part of the hæmoglobin molecule, the latter should show diminution: Masoin[99] found that "the relative quantity of oxyhæmoglobin in the blood was diminished in proportion as the morbid results of thyroidectomy progressed." That the thyroid should be able to influence metabolism under these conditions is evident; that it does so is made apparent by the following testimony:—

Swale Vincent[100] published some years ago such a succinct and withall comprehensive review of the subject that excerpts from his text will be submitted as evidence:—

"The discovery of iodine in the thyroid gland by Baumann[101] and the isolation of thyroiodin as the probable active principle led observers to test the action of this last upon metabolism. Treupel,[102] Grawitz,[103] David,[104] and Dinkler,[105] by observations on the human subject, and Roos,[106] who used a small dog, came to the conclusion that thyroiodin influenced metabolism in the same way as the thyroid gland substance itself, in that the body weight diminished and the nitrogen secretion increased.

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[98] Albertoni and Tizzoni: Cited by Maragliano: Gaz. degli Osped., Oct. 28, 1894.

[99] Masoin: Bull. de l'Acad. de méd. de Belgique, No. 1, p. 33, 1895.

[100] Swale Vincent: Lancet, Aug. 18, 1906.

[101] Baumann: Zeit. f. physiol. Chemie, Bd. xxi, S. 319, 1895.

[102] Treupel: Münch. med. Woch., Bd. xliii, Nu. 6, S. 117, 1896, and Nu. 38, S. 884.

[103] Grawitz: *Ibid.*, Bd. xliii, Nu. 14, S. 312, 1896.

[104] David: Zeit. f. Heilkunde, Bd. xvii, S. 439, 1896.

[105] Dinkler: Münch. med. Woch., Bd. xliii, Nu. 32, S. 512, 1896.

[106] Roos: Zeit. f. physiol. Chemie, Bd. xxi, S. 19, 1895.

"Some experiments of short duration are recorded, directed to the estimation of the oxygen taken in and the carbon dioxide given out during thyroid administration. These respiration experiments were carried out after the Zuntz-Geppert method. Magnus-Levy[107] found in a normal man during the exhibition of thyroid glands a not very distinct increase of the oxygen intake and the carbonic acid output. Later experiments by the same author[108] on a myxœdematous patient gave, on the other hand, an increase of 80 per cent. in the oxygen intake under the influence of thyroid, and 43 per cent. under the influence of iodothyrin.

"The experiments of Stüve[109] on a healthy man showed an increase of oxygen intake of 20-23 per cent., and a somewhat smaller increase of carbon dioxide excretion. Thiele and Nehring[110] also found an increase of oxygen intake amounting to 20 per cent.; the carbon dioxide output was smaller and irregular. . . . . Schöndorff[111] has performed a series of very careful experiments of long duration upon dogs, and has reached the conclusion that metabolic processes are distinctly increased by the administration of thyroid substance. There is at first no influence on proteid metabolism, but an increase in nitrogenous excretion from increased elimination of nitrogen-holding extractives already present in the body. The body fat is first used up. After a certain period, however, the proteid is also attacked. On stopping the thyroid administration, the metabolism returns to normal, while renewed administration leads to increased nitrogenous excretion."

This occurs likewise when the thyroid gland is overactive, as in exophthalmic goiter. Hirschlaff[112] found the "metabolic processes most surprisingly active." In one case the gaseous interchange was found 77 per cent. greater than that of a normal girl of about the same weight. Salomon[113] also found the O intake decidedly increased. Scholz[114] found that when thyroid extract was administered to such a case the excretion of *phosphoric acid was increased tenfold, while in a normal subject the increase was only 25 per cent.* The great increase of O intake is often such as to cause considerable discomfort, which the patient describes as "flushings," "hot waves," etc. The emaciation, rapid breathing, duskiness, muscular cramps, etc., also point to excessive oxygenation.

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[107] Magnus-Levy: Berl. klin. Woch., Bd. xxxii, S. 650, 1895.

[108] Magnus-Levy: Deut. med. Woch., Bd. xxii, Nu. 31, S. 491, 1896.

[109] Stüve: Festschrift des Städtischen Krankenhauses in Frankfurt am Main, Sept., 1896.

[110] Thiele and Nehring: Zeit. f. klin. Med., Bd. xxx, S. 41, 1896.

[111] Schöndorff: Pflüger's Arch., Bd. lxvii, S. 395, 1897.

[112] Hirschlaff: Zeit. f. klin. Med., Bd. xxxvi, Hft. 3-4, S. 200, 1898-99.

Easterbrook,[115] after a careful study of the influence of thyroid extract in a large number of cases of various kinds, concluded that "thyroid is a profound catabolic stimulant," and that "it greatly accelerates the splitting up and oxidation of the tissues." Administered in exophthalmic goiter (before the cachectic or breaking-down period) thyroid extract should prove harmful. Tyson,[116] referring to Greenfield, states that "thyroid in excess produces tachycardia, tremor, headache, sweating, and prostration, symptoms of Graves's disease," and that "when administered during the disease, it aggravates the symptoms." This applies also to parathyroid extracts. James J. Walsh[117] concludes, after using the latter, "I do not think that parathyroid extract produces any benefit in cases of Graves's disease, and that if employed in large doses, even for a few days, or in small doses for many days, it will produce an exacerbation of symptoms not unlike those which are produced by the ingestion of a certain amount of thyroid substance."

All this shows clearly the marked influence of the thyroparathyroid apparatus upon the intake of oxygen, the output of carbon dioxide, phosphoric acid, nitrogen, etc., *i.e.*, upon metabolism—precisely the function carried on by the adrenals through the intermediary of the anterior pituitary.

That overactivity of the anterior pituitary is capable of causing excessive metabolism and overnutrition, is emphasized by the osseous and muscular overgrowth that occurs in the erethic stage of acromegaly. Marie termed this disease a "systemic dystrophy" of pituitary origin, while Tamburini, Harlow

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[113] Salomon: Berl. klin. Woch., Bd. xli, S. 635, 1904.
[114] Scholz: Centralbl. f. inn. Med., Bd. xvi, S. 1041, 1069, 1895.
[115] Easterbrook: Lancet, August 27, 1898.
[116] Tyson: "Practice of Medicine," third edition, p. 672, 1903.
[117] James J. Walsh: Amer. Med., May 20, 1905.

Brooks, and Mitchell and Le Count, as stated in the first volume, and more recently by D. D. Lewis[118] have shown, not only that the anterior lobe was the seat of the lesion, but that the latter was due to "hyperplasia of the chromophile cells"—a suggestive condition in view of my interpretation of the functions of this organ. Benda's[119] conclusion (1891) that this probably indicates "an excessive activity of the gland," Woods Hutchinson's[120] belief that the pituitary "is the growth center or at any rate the proportion regulator of the skeleton," indicate that, although unaware of the nature of the process, investigators have connected the pituitary with nutrition. This applies as well to the question in point: Fuchs[121] remarks in a study of the tumors of the pituitary: "Very important in this connection is the influence exerted by the pituitary upon the bodily metabolism."

Besides its direct action on all tissue cells, the thyroid secretion can, through the anterior pituitary and the adrenals influence general oxidation. Here again, the prevailing obscurity as to the manner in which thyroid extract influences metabolism affords in itself cogent testimony in favor of an interpretation which accounts so readily for recorded experimental and clinical facts. This becomes all the more evident when we realize that physiologists have failed to explain metabolism, as shown by Foster's previously quoted conclusion that, after all, it "consists of guesses and gaps." With the thyroid apparatus as the source of a secretion which sustains the functional activity of the anterior pituitary, *i.e.*, of the sensory test-organ which governs the adrenals, and with the adrenal secretion as the active factor in metabolism, with the systemic thyroid secretion sustaining catabolism, we have a chain of solidly forged links.

The functional relationship between the thyroid, the anterior pituitary body, and the adrenals is further shown by the fact that each of these organs, when overactive, can provoke glycosuria. I pointed out this fact in the first volume[122] and submitted additional evidence in the present volume[123] as to the rôle of the pituitary and adrenals. The supplementary evidence concerning that of the thyroid need alone, therefore, be adduced.

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[118] D. D. Lewis: Johns Hopkins Hosp. Bull., May, 1905.
[119] Benda: Cited by Lewis: *Ibid.*
[120] Woods Hutchinson: Osler's "Practice of Medicine," p. 1143, 1906.
[121] Fuchs: Wien. klin. Woch., Bd. xvi, S. 151, 1903.
[122] *Cf.* vol. i, pp. 282 to 420, in the first three editions.
[123] *Cf.* this vol., p. 1021.

That overactivity of the thyroid can cause glycosuria is shown by the fact that it is commonly observed in exophthalmic goiter, a disease in which the thyroid is admittedly overactive. In some cases, in fact, glycosuria occurs prior to the development of the more typical symptoms of the disease, exophthalmos, enlargement of the thyroid, etc. Cases in which the sugar occurs as a symptom of the general disease—those which interest us in the present connection—have been reported by Lauder Brunton,[124] Barnes,[125] Launois,[126] who refers to twenty-six cases reported by others, including two by Lépine, Souques and Marinesco,[127] Kleinwächter,[128] Pitres,[129] and many other clinicians.

That irrespective of such diseases, overactivity of the thyroid can provoke glycosuria has moreover been pointed out by Arnold Lorand,[130] who found that thyroid extract exceeded adrenal extract in activity in this particular, and that it could bring on glycosuria, "and even its higher degree, true diabetes." Bosanquet[131] observed a case of combined "diabetes and myxœdema." Many such have been reported; but this is not true diabetes: it is the form in which, as I have previously shown,[132] the ingested sugar is absorbed and eliminated without first becoming converted into glycogen. It may also occur, in fact, in the terminal or cachectic stage of acromegaly.[133] But this does not, in the least, invalidate the fact that overactivity of the thyroid also evokes glycosuria by causing indirectly a too active conversion of glycogen into sugar. Lorand found that "by giving thyroid extract all the symptoms of true diabetes could be produced," and refers to cases recorded by Ewald[134] and Béclère,[135] in which diabetes was brought on by "treatment with large doses of thyroid extract."

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[124] Lauder Brunton: St. Bartholomew's Hosp. Reports, vol. x, p. 253, 1874.
[125] Barnes: Brit. Med. Jour., June 1, 1889.
[126] Launois: Lyon méd., vol. xxix, p. 46, 1897.
[127] Souques and Marinesco: Bull. méd., June 16, 1897.
[128] Kleinwächter: Centralbl. f. Gynäcol., Bd. xvi, S. 181, 1892.
[129] Pitres: Le bull. méd., Aug. 18, 1897.
[130] Arnold Lorand: Ann. de la Soc. roy. d. sc. méd. et nat. de Bruxelles, T. xii, fasc. 4, 1903; Trans. Pathol. Soc. of London, vol. lvii, Pt. 1, 1906; Monthly Cyclo. of Pract. Med., Aug., 1906.
[131] Bosanquet: Lancet, June 10, 1905.
[132] *Cf.* vol. i, p. 418, in the first three editions.
[133] *Cf.* also vol. i, pp. 154, 197, 365, in the first three editions.
[134] Ewald: Berliner klin. Woch., Bd. xxxii, ii, S. 26, 55, 1895.

That a functional link exists between the thyroid and the anterior pituitary body in this connection is well shown by the fact that in cases of acromegaly (the true form of which is due to hypertrophy of the anterior pituitary only, as shown by Tamburini,[136] Harlow Brooks,[137] Lewis and others) in which diabetes is present, the thyroid is also found "hypertrophied, with much colloid," as illustrated by cases reported by Pineles,[138] Hansemann,[139] Ferrand,[140] Harlow Brooks,[141] Dallemagne,[142] and others.[143] Indeed, Lancereaux[144] and others have reported cases in which acromegaly, exophthalmic goiter and glycosuria were present simultaneously.

Once more are we confronted with a condition, the pathology of which has remained obscure. Tyson,[145] for example, states, referring to diabetes, that "there is no disease concerning which so much accurate knowledge has been arrived at. and of the true pathology of which we are so thoroughly in the dark." An overactive thyroid, by exciting the anterior pituitary and through its test-organ, the adrenals, accounts clearly for at least one way in which it can be produced. (We will see elsewhere that many drugs and poisons can cause it by exciting directly the test-organ.) As previously shown, the investigations of Blum, Croftan, Herter and others have demonstrated that adrenal extractives produce glycosuria.

Now that the relationship between the thyroid and tissue metabolism, *i.e.*, the vital process—through the intermediary of the anterior pituitary and the adrenals—has been shown, many clinical facts find a logical explanation which so far have only been accounted for by tentative hypotheses devoid of foundation.

Osler and Norton[146] state that "thyroid extract has revolutionized the treatment of cretinism," and that such "children show a most astonishing rapidity of growth during the first months or a year of treatment," after which "growth proceeds gradually as in healthy children," along with development of the intelligence, the adjustment of functions to the normal, etc. Now, in this disease, as in myxœdema, its kindred disorder in adults, the vital processes are not carried on with sufficient activity, and—in the light of my views—thyroid extract, by stimulating the adrenal center, raises all vital functions to their normal standard by promoting general nutrition. Hence also, the value of thyroid extract: in arrested growth, irrespective of cretinism, as shown by Hertoghe,[147] Schmidt,[148] and others; for delayed union in fractures by Gauthier,[149] Bayon,[150] and others; chronic osteomyelitis by W. J. Taylor,[151] etc., and other conditions in which the vital and reparative processes are sluggish.

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[135] Béclère: Gazette méd. de Paris, 1899; cited by Lorand: *Loc. cit.*
[136] Tamburini: Riv. Sperm. de Fren., p. 559, 1894; p. 414, 1895.
[137] Harlow Brooks: Arch. of Neurol. and Psych., vol. i, p. 485, 1898.
[138] Pineles: Jahrbuch der Wiener Krankenanstalten, pp. 256, 263, 1897; cited by Lorand: Monthly Cyclo. of Pract. Med., Sept., 1906.
[139] Hansemann: Berl. klin. Woch., Bd. xxxiv, S. 417, 1897.
[140] Ferrand: Revue neurologique, T. ix, p. 271, 1901.
[141] Harlow Brooks: *Loc. cit.*
[142] Dallemagne: Archives de méd. expérimentale, etc., T. vii, p. 589, 1895.
[143] Cited by Lorand: *Loc. cit.*
[144] Lancereaux: La semaine médicale, Feb. 3, 1895.
[145] Tyson: *Loc. cit.*, p. 797.
[146] Osler and Norton: *Loc. cit.*, p. 496.

All this is further emphasized by the influence of thyroid extract upon accumulated wastes, fats, etc. In enhancing metabolism, it naturally promotes destruction of these substances; in other words, as stated by Easterbrook, thyroid extract is "a profound catabolic stimulant"; hence its marked action in obesity as shown by Charrin,[152] Magnus-Levy,[153] and many other clinicians, and its special efficacy as observed by French physicians in subjects that are also "pale, soft and flabby." By stimulating metabolism, the fats are caused to break down—the first manifestation of adequate oxygenation.

This applies as well to toxic wastes which accumulate when metabolism is inadequate—a fact which accounts for the relief afforded by thyroid extract in the tetany that follows removal of the thyroid gland. The absence of thyroid secretion which this operation entails, by depriving the test-organ of its normal stimulus, reduces the secretory activity of the adrenals in proportion; the oxygenation of the entire organism being correspondingly impaired, the food and tissue wastes are inadequately catabolized and accumulate in the blood, finally causing convulsions. Herbivora, rabbits, sheep, oxen, horses, etc., whose food contains much less nuclein and other substances capable of forming toxic wastes, suffer less from tetany than carnivorous animals, cats, dogs, foxes, men, etc., whose food contains considerable of these noxious and spasmogenic bodies. Even in the latter animals, however, thyroid extract arrests the convulsions.

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[147] Hertoghe: Bull. de l'Acad. roy. de méd. de Belgique, p. 897, 1895.
[148] Schmidt: Therap. Woch., Nov. 15, 1896.
[149] Gauthier: Lyon méd., vol. lxxxv, pp. 296, 359, 1897.
[150] Bayon: Verhandlungen des phys. méd. Gesellsch. zu Würzburg, Bd. xxxv, S 240, 1903.
[151] W. J. Taylor: Monthly Cyclo. of Pract. Med., July, 1905.
[152] Charrin: Semaine méd., Jan. 2, 1895.
[153] Magnus-Levy: Zeit. f. klin. Med., Bd. xxxiii, Hft. 3-4, S. 269, 1897.

The thyroid gland has long been known to neutralize or destroy toxic wastes, its secretion being thought to do so while circulating in the blood by some authorities, while others hold that this process is carried on in the organ itself. These views, however, have not been satisfactorily sustained. On the other hand, excitation of the adrenal center in the anterior pituitary—the test-organ—and the resulting increase of the blood's oxygenizing (and therefore, catabolic) activity, accounts clearly for the beneficial effects observed *as long as the extract is administered.*

This explains also the beneficial and sometimes curative effects of thyroid extract in the tetany of gastroenteritis, especially in children, and idiopathic tetany as shown by Gottstein,[154] Maestro,[155] Levy-Dorn,[156] and other observers. While the spasmogenic toxics here are derived directly from imperfectly digested food-stuffs, the fact that toxic waste products are likewise destroyed under the influence of thyroid extract is shown by its marked action in puerperal eclampsia. This was first shown by Nicholson,[157] whose aim was to antagonize "auto-intoxication," thyroid proving curative when given in large doses. Nicholson's results have been corroborated by other observers.

Here again we have evidence of concomitant overactivity of the anterior pituitary. Lange[158] found in a study of 133 cases, that the thyroid gland begins to enlarge during the fifth or sixth month of pregnancy and that eclampsia and albuminuria occurred most frequently among cases (22) which did not show this enlargement. This indicates—in the light of my views—overactivity of the organ at a time when the wastes of the fœtus are such as to increase materially those of the mother, the object being to enhance the catabolic activity of the blood correspondingly. Hence the beneficial influence of thyroid extract observed by Nicholson and others. That the anterior pituitary is the seat of a corresponding overactivity during pregnancy is shown by Comte,[159] who specified that "the hypertrophy affected the glandular lobe alone." Launois and Mulon[160] confirmed these observations and emphasize "the disproportion between the two lobes of the gland, the epithelial lobe being much larger, in comparison with the neural lobe, than under normal conditions." Histological examination of the organs showed, moreover, that they were "in a manifest state of hyperactivity."

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[154] Gottstein: Deut. Zeit. f. Nervenheilk., Bd. vi, S. 177, [illegible].
[155] Maestro: Riforma Medica, vol. xii, ii, p. [illegible], [illegible].
[156] Levy-Dorn: Berl. klin. Woch., Bd. xxxiii, S. [illegible], [illegible].
[157] Nicholson: Scottish Med. and Surg. Jour., vol. viii, p. [illegible], 1901; vol. xii, p. [illegible], [illegible].
[158] Lange: Zeit. f. Geburts. u. Gynäk., Bd. xl, S. 34, [illegible].

As will be shown under their respective headings, thyroid extract has also proven beneficial in such disorders as epilepsy, tetanus, rheumatoid arthritis, etc., in which, as in eclampsia, toxic wastes are the pathogenic elements—all through its stimulating action upon the test-organ, *i.e.*, the adrenal center.

Adrenal extract, adrenalin, etc., have also proven effective —due allowance being made for its ephemeral action—in disorders characterized by deficient oxygenation, hypocatabolism, etc.

We have seen that adrenal extract and adrenalin provoked glycosuria: the increase of metabolic activity in the pancreas, and the resulting overproduction of amylopsin—the ferment which acts on glycogen—account for the phenomenon. The familiar action of adrenal on the tissues is also explained by the intense metabolic activity which it excites in the cellular elements, owing mainly to its identity as a catalytic—a fact which explains also the observation of Herter that glycosuria could be produced by applying a solution of adrenal into the pancreas. The vascular contraction it produces—thus insuring a bloodless field for operation—is also a normal outcome of the excessive metabolism it induces in the muscular elements of the vessels. This acounts for the production of arteriosclerosis by adrenal extractives, as shown by Josué,[161] Erb,[162] von Rzentkowski,[163] and others, since excessive constriction of the vasa vasorum must normally produce denutrition of the vascular coats, with degeneration and fibrosis as results. Thus Councilman,[164] in a study of forty-one autopsies, found that in the nodular form the primary alteration consisted "in a degeneration or a local infiltration in the media and adventitia, chiefly about the vasa vasorum."

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[159] Comte: Thèse de Lausanne, 1898.
[160] Launois and Mulon: Ann. de gynéc. et d'Obstét., Jan., 1904.

The usefulness of adrenal extract and adrenalin in conditions due to depression of vital activity, hypocatabolism, etc., likewise finds a logical explanation. In shock, a condition in which, as stated by Kinnaman,[165] "the most uniform and progressive factor" is "the fall in temperature," adrenalin, as shown by Crile,[166] is of great value when judiciously employed. This investigator resuscitated animals by its use—with simultaneous artificial respiration—fifteen minutes after life had ceased—a normal result in the light of my opinion, since the adrenal secretion sustains the vital process in the tissue cells. In cases of asthma with lowered vasomotor tone S. Solis-Cohen[167] and Bullawa and Kaplan[168] found it effective: so did Mankovsky,[169] Floersheim,[170] and others, in cardiac weakness and threatening collapse—especially, according to Boy-Teissier,[171] when there is dilatation and cyanosis. These are but few of the conditions in which adrenal extractives have been tried successfully. Here, however, as in other disorders, they have proven effective only where the life-processes were more or less in abeyance.

On the whole, we have now seen that the thyroid gland, the anterior pituitary and the adrenals influence temperature and metabolism in the same way, and that they awaken homologous phenomena in many directions. That each of these structures is capable of provoking individually such parallel effects would be illogical; indeed, no experimentally-sustained explanation would be available to account for them. On the other hand, when the three sets of organs are considered as related functionally, *i.e.*, as the adrenal system, the phenomena awakened by each organ occur as normal results of its action upon the organ with which it is linked. Thus, the thyro-parathyroid secretion enhances metabolism by exciting the anterior pituitary body, owing to the presence in the latter of its sensitive test-organ; the anterior pituitary in turn produces the same effect by stimulating the adrenals through the nerve-path which unites it with these glands; finally, the adrenals also sustain metabolic activity through their secretion, the precursor of adrenoxidase. Of the latter substance I have had occasion to say:[172] "It is able not only to endow nonliving though viable proteids with vitality by bringing into play and governing the activity of various other physico-chemical bodies, but it can also sustain the vital process it has initiated in all the cells of an organism." Recalling now that it is through the intermediary of leucocytes laden with exogenous products that the secretions elaborated in the thyroid and the parathyroids can produce such effects, and that toxic wastes are destroyed when excess of adrenoxidase appears in the blood, we obtain an insight into the means through which the body protects itself against disease, *i.e.*, of the *vis medicatrix naturæ.*

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[161] Josué: C. r. de la Soc. de biol., vol. lv, p. 1374, 1903.
[162] Erb: Wien. med. Presse, Bd. xlv, Nu. 18, S. 854, 1904.
[163] von Rzentkowski: Berl. klin. Woch., Bd. xli, S. 830, 1904.
[164] Councilman: Osler's "Practice of Medicine," p. 771, third edition, 1898.
[165] Kinnaman: Annals of Surg., Dec., 1903.
[166] Crile: Boston Med. and Surg. Jour., Mar. 5, 1903.
[167] S. Solis-Cohen: Jour. Amer. Med. Assoc., May 12, 1900.
[168] Bullawa and Kaplan: Med. News, Oct. 24, 1903.
[169] Mankovsky: Russian Archives of Path., Clin. Med. and Bact., Mar., 1898.
[170] Floersheim: N. Y. Med. Jour., Oct. 6, 1900.
[171] Boy-Teissier: Arch. gén. de méd., Aug. 23, 1904.

On the whole, in addition to the direct action of the thyroid apparatus on the tissues of the body at large: (1) *the thyroid apparatus (the thyroid and parathyroids), the anterior pituitary body and the adrenals are functionally interdependent and thus constitute the adrenal system;* (2) *the function of the thyroid apparatus is to supply a secretion to the blood which enables the latter, while circulating through the anterior pituitary body, to excite its test-organ;* (3) *the function of the test-organ is to react sufficiently under the influence of the thyro-parathyroid secretion, to stimulate the adrenals and thus to sustain their secretory efficiency;* (4) *the function of the adrenals is to sustain oxygenation and therefore general metabolism—the vital process—by means of its oxygen-laden secretion, adrenoxidase;* (5) *if from any cause the functional activity of either one of the organs composing the adrenal system becomes inade-*

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[172] *Cf.* this vol., p. 983 *et seq.*

quate or excessive, general metabolism, and therefore the vital process, is influenced accordingly. Hence, (6) *the functions of the adrenal system are (a) to sustain general metabolism and the vital process, (b) to protect the organism, when toxic wastes accumulate in the blood, by augmenting the proportion of adren-oxidase supplied to the blood and therefore the antitoxic activity of the latter;* (7) *the adrenal system, therefore, is the body's auto-protective or auto-immunizing mechanism.*

THE THYRO-PARATHYROID SECRETION AS THE SENSITIZING SUBSTANCE OF ALL CELLS AND AS THE PHYSIOLOGICAL EXCITANT OF THE TEST-ORGAN.

As stated in the preceding section, the experiments of Gley, Moussu, and Vassale and Generali showed that the thyroid fulfilled trophic functions, while extirpation of the parathyroids was followed by convulsive phenomena. This is sustained by a large number of experiments in animals and many clinical observations. In young dogs, for instance, extirpation of the thyroid alone provokes all the phenomena of cretinism; as stated by Jeandelize[173] "the animals remain small, become apathetic; the face becomes wrinkled, the trunk broad, the belly rounded, the skin thickened and lobulated owing to myxœdematous infiltration, and the fur rough." Briefly, thyroidectomy pure and simple provokes trophic disorders. Although Kishi[174] has shown that dogs and cats may die after this procedure even though the parathyroids are left intact, the fact remains that even in carnivorous animals, including man, extirpation of the thyroid proper is not usually followed by death, but by the cachexia strumipriva of Reverdin and Kocher, *i.e.*, myxœdema.

Removal of both the thyroid and parathyroids, on the other hand, is generally fatal. Jeandelize collected 427 experiments of this kind on record, all in dogs. The mortality was 91.6 per cent. Edmunds[175] states that this procedure causes "almost invariably the following symptoms: tremors, convulsive attacks with rapidity of breathing and rigidity of limbs passing into paralysis. Death comes on within a few days, usually in less than a week." The same writer says also, however: "The excision of the four parathyroids only, leaving the thyroid proper, generally causes the *same symptoms* with the *same termination*. Indeed, Vassale and Generali[176] lost all their nine dogs in eights days; Moussu,[177] all of his eighteen dogs in from two to forty-six days; Lusena,[178] all of his nineteen dogs in three days. Edmunds,[179] however, lost only four out of nine. Vincent and Jolly[180] found also that parathyroidectomy was not necessarily fatal. Be this as it may, the seriousness of the procedure is self-evident; the mortality approximates at least that which follows removal of the thyroid and parathyroids.

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[173] Jeandelize: *Loc. cit.*, p. 41.
[174] Kishi: Virchow's Archiv, Bd. clxxvi, S. 260, 1904.
[175] Edmunds: Practitioner, Apr., 1901.

This confirms the opinion first advanced by Gley[181] as far back as 1891, that the parathyroids are decidedly the most active organs of what he has termed the "thyroid apparatus." The reason for this became apparent when he found, as we have seen, that the secretion of the parathyroids differed from that of the thyroid in that it contained six times more iodine in the dog, and twenty-five times more in the rabbit. Although these relative proportions are doubtless subject to great variations, they nevertheless suggest that the parathyroids are the source of the principle which endows the secretion of the thyroid with the greater part of its activating or rather energizing property—probably, owing to the comparatively large proportion of iodine it contains.

A striking feature concerning iodine is its uniform presence in organic matter in combination with sodium, potassium, calcium, and magnesium. In the seas it is found in abundance in marine plants, especially the algæ. Spring water was also found by Chatin[182] to contain iodine, but not at the spring itself, and only in water that had followed a course strewn with fragments of organic matter, animal and vegetable. It is also present in the soil. Daubrée[183] found it in the thermal waters of Bourboule-les-Bains, and many mineral waters are known to contain it. While all waters in which iodine is present tend to eliminate it (hence the greater quantity of iodine at the sea-shore than elsewhere, and in rain-water) all living cells, animal or vegetable, have a marked affinity for it. That it is an important constituent of the living organism is shown by the fact that all marine animals contain more or less of it, the European oyster and the cod probably the largest proportion. Fresh-water fishes, crustaceans and batrachians also show distinct evidence of its presence. We have seen that our blood is after all but a bit of the ocean circulating in our vessels and that, as stated by Claude Bernard, our cells live therein as fishes do in water.

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[176] Vassale and Generali: Arch. ital. de Biol., T. xxv, p. [illegible], 1896.

[177] Moussu: C. r. de la Soc. de biol., Jan. 16, 1897.

[178] Lusena: "Fisio-patologia dell 'apparecchio tiro-paratiroideo," Florence, [illegible].

[179] Edmunds: Jour. of Pathol. and Bact., May, [illegible].

[180] Vincent and Jolly: Jour. of Physiol., vol. xxxii, p. 65, 1904.

[181] Gley: C. r. de la Soc. de biol., p. 843, 1891.

[182] Chatin: Cited by Trousseau and Pidoux: "Traité de Thérap," vol. i, p. 227, 1875.

[183] Daubrée: Cited by Dana: "Manual of Geology," pp. [illegible] and [illegible], fourth edition, [illegible].

Chittenden,[184] however, justly urges that "the iodine in iodothyrin is certainly not active as iodine; the amount is too small." How then does it act?

Suggestive in this connection is the fact that the thyro-parathyroid secretion embodies not only the compounds that we found in the digestive leucocytes, but also nucleo-proteid and adrenoxidase.

Some years ago, Halliburton[185] in the course of a paper on the internal secretions, remarked: "Among the earliest to investigate the proteids of the thyroid was Bubnow,[186] and to one of these, thyreo-proteid, Notkin[187] attributes the activity of the organ. He considers that its action resembles that of an enzyme or *unorganized ferment.*" In a foot-note the author states that "the ferment-theory is also urged by White and Davies." Again: "An investigation of the thyroid-proteids was later made by Gourlay[188] under my supervision, and his conclusions are as follows: The only proteid that can be obtained in any quantity from the thyroid is a *nucleo-proteid;* this is derived, at any rate in part, from the *colloid* material in the acini." Halliburton says in this connection, that nucleo-proteid "is proteid in combination with nuclein, the phosphorus-rich constituent of nuclei, but which is also found in the protoplasm of cells"—thus proving that we are dealing with the compound we found elsewhere. Finally, he states that "Hutchison[189] confirms Baumann's theory that the activity of the organ is accounted for by its proteid iodine-containing constituents; after removal of the proteids, thyroid extracts are of no use."

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[184] Chittenden: Trans. Congr. of Amer. Phys. and Surgs., vol. iv, p. 161, 1897.

[185] Halliburton: Practitioner, Jan., 1897.

[186] Bubnow: Zeit. f. physiol. Chemie, Bd. viii, S. 1, 1884.

[187] Notkin: Wien. med. Woch., Bd. xlv, S. 834 u. 872, 1895.

[188] Gourlay: Jour. of Physiol., vol. xvi, p. 23, 1894.

The last sentence shows clearly that iodine is not the only factor in the action of the secretion and that its influence partly depends upon the presence of the proteid—with which, as we have seen in the fourteenth chapter, all ferments are intimately combined. Notkin's observation that the action of the secretion resembled that of a ferment, and the fact, shown by myself, that *all* the ferments of the organism owe their activity to the "ferment of ferments," the active principle of the adrenal secretion—that embodied in adrenoxidase—all point to the presence of the latter in the thyro-parathyroid secretion. Indeed, we have seen that adrenoxidase, corpuscular and plasmatic, is a globulin. Now, R. Hutchison[190] states that the colloid consists of two proteids: "One of these, which makes up *by far the larger part of the secretion,* resembles closely in its behavior the class of proteids spoken of as *globulins;* the other is a nucleo-proteid." He also[191] found that besides containing phosphorus and being rich in iodine, the colloid contained sulphur, an element which, as stated by Gamgee[192] in reference to hæmoglobin, "belongs to the albuminous part of the molecule," *i.e.*, to adrenoxidase. The iodine is evidently bound up with the latter, for Baumann[193] found his iodothyrin in the albumins of the gland as "thyro-*iodoglobulin* or thyro-*iodoalbumin.*" Oswald[194] also isolated a body he termed *thyreoglobulin,* which constituted about 10 per cent. of the gland and contained 14.3 per cent. of iodine and which was found to increase metabolism, and nitrogen excretion, etc.

Briefly, the thyro-parathyroid secretion differs only from the proteolytic triad distributed by leucocytes to all the cells in the organism, in that it contains iodine—9.3 per cent. in Baumann's thyroidin, 14.3 in Oswald's thyreoglobulin—closely bound up with adrenoxidase. As Chittenden says, iodine is certainly not active as such. In fact, Toepfer[195] has shown that one ounce of sheep's thyroid contains but 0.009 ($^1/_7$ grain) of this halogen. The foregoing facts point to its mode of action, viz., that of a "ferment" as stated by Notkin—a triad, from my point of view, in which iodine plays the part of preferment.

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[189] Hutchison: Brit. Med. Jour., Mar. 21, 1896; Jour. of Physiol., vol. xx, p. 474, 1896.

[190] R. Hutchison: Practitioner, April, 1901.

[191] Hutchison: Jour. of Physiol., vol. xx, p. 474, 1896.

[192] Gamgee: Schäfer's "T. B. of Physiol." vol. i, p. [illegible], 1898.

[193] Baumann: *Loc. cit.*

[194] Oswald: Münch. med. Woch., Bd. xlvi, S. 1073, 1899.

What is the physiological action of this iodine triad or "ferment"?

Levene,[196] Justus,[197] and others found iodine in practically all tissues. Gley[198] held that the iodine found in the thyroid is derived from the blood, his researches having shown that the red corpuscles stored it. We have seen, however, that iodine is not taken up by these cells, but, as observed by Labbé and Lortat-Jacob, by leucocytes. The phenomena of iodophilia also show that these cells are prone to absorb this halogen. Its presence in the red corpuscles, however, when considered in the light of my views, is subject to an interpretation other than that advanced by Gley:—

In the preceding chapter, we followed the secretions of the thyroid and parathyroids to the heart, where they entered the general venous circulation jointly, and thence to the pulmonary alveoli. In the first three editions[199] I submitted data which had led me to suggest that the eosinophile leucocytes (which are often found in the sputum in asthma, tuberculosis, etc., and are thought by various authors to take part in the formation of the alveolar epithelium[200]) built up hæmoglobin—its iron-containing portion, hæmatin—with iron derived from the intestine, and carried it to the pulmonary alveoli. Here, I held, the cells secreted their product into the adjacent plasma, where it was "absorbed by the underlying red corpuscles along with the oxygenized secretion" of the adrenals, *i.e.*, adrenoxidase. I was not aware at the time that the eosinophiles had already been associated with this function by Hayem, who described them as the "hæmoglobinic cells."[201] Under these conditions, the process through which the thyro-parathyroid secretion enters the red corpuscles is self-evident: being likewise present in the plasma underlying the aveoli, it is absorbed with the hæmoglobin and its albuminous moiety, adrenoxidase, and distributed with the latter throughout the body. Hence the secretion is distributed by the red corpuscles to all cells and to the plasma itself.

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[195] Toepfer: Lancet, Mar. 7, 1896.
[196] Levene: Arch. of Neurol. and Psychopath., vol. ii, p. 571, 1899.
[197] Justus: Virchow's Archiv, Bd. clxxvi, S. 1, 1904.
[198] Gley: Semaine méd., May 25, 1898.
[199] *Cf.* vol. i, p. 716, in the first three editions.
[200] Lenhartz: "Clinical Micros. and Chem.," transl. by Brooks, 1904.
[201] Hayem: Cited by Levaditi: *Loc. cit.*, p. 36.

The marked influence of the thyro-parathyroid secretion on metabolism suggests that it is more potent in the vital process than adrenoxidase itself. That such is not the case, however, is shown by the fact that removal of the thyroid and parathyroids does not always cause death. We have seen that Edmunds lost but four out of his nine dogs. Vincent and Jolly[202] were also led experimentally to conclude that "it cannot be truly said that either thyroids or parathyroids are essential for life, since it is frequently possible to remove either or both without causing death," although they fully recognize "as others have done, that fatal results, when they occur, are not due to injuries to surrounding structures accompanying the surgical interference, but must be referred to absence of the glands in question." Again, if the thyro-parathyroid secretion were the chief factor in sustaining the cellular interchanges, removal of the pituitary body or of the adrenals would only give rise to trophic disorders and seldom if ever prove fatal; whereas, in the great majority of instances, death occurs within a few days. This fact in itself, however, affords a clue to the rôle of the secretion. As a large number of experiments have shown, carnivorous animals are readily killed by thyro-parathyroidectomy while many herbivorous animals survive. Moreover, if carnivorous animals are fed on milk only, after the operation, the post-operative life is greatly prolonged. It is plain, therefore, that the influence of the thyro-parathyroid secretion is connected in some way with toxic wastes (which are proportionally much greater under a meat diet than under a vegetable diet) and that this influence is exercised not only, as we have seen, upon the cellular elements of the anterior pituitary, but upon all cells.

The close association of the thyro-parathyroid secretion with adrenoxidase, which led Oswald to term the thyroid secretion "thyroglobulin," corresponds with a constituent of the blood to which I have referred to in the preceding volume, viz., Sir A. E. Wright's *"opsonin,"* a substance which renders micro-organisms vulnerable to phagocytes.

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[202] Vincent and Jolly: Jour. of Physiol., vol. xxxii, p. 65, 1904.

Denys and Leclef,[203] in 1895, showed experimentally that leucocytes were able to ingest bacteria only after the latter had been prepared, so to say, by the action of some substance in the blood-plasma. Thus, while the blood of a normal rabbit failed to destroy the streptococcus pyogenes, that of a vaccinated rabbit delayed the multiplication of these germs and sometimes destroyed them. Such a rabbit could stand with impunity a dose of streptococcus sufficient to cause erysipelas in a normal animal. Now, leucocytes from the latter, though unable to destroy streptococci, destroyed actively these germs in the blood of the vaccinated animal, while blood from the latter, when added to that of a normal animal, also caused the leucocytes of this animal to become energetically bactericidal. This shows plainly that the plasma of a vaccinated animal contains a substance which either increases the vulnerability of the germs to phagocytosis or the activity of the phagocytes. Two years later, Mennes[204] noted that the immunity conferred on guinea-pigs with toxins or pneumococcus cultures was due to a change in their serum which increased markedly the activity of phagocytosis, though the phagocytes themselves were not directly influenced. Wright and Douglas[205] termed this substance "opsonin" and showed that it was a constituent of the serum or plasma. They likewise concluded that it prepared the bacteria for phagocytosis without acting on the leucocytes. Neufeld and Rimpau[206] also found in the plasma a substance which "sensitized" bacteria without influencing the leucocytes. Virulent streptococci and pneumococci which failed to be ingested by the latter when they had been previously treated to anti-streptococcic serum, were immediately taken up by these cells when the germs had themselves been treated to this serum, though the leucocytes had not. Many other experimenters have confirmed these observations without, however, throwing light upon the nature of the process. Moreover, as emphasized, by Potter, Ditman and Bradley:[307] "Up to the present time very little has been determined concerning the source of the opsonins," and, referring to the above-named investigators, they state that they have all shown that "the opsonins exist in the blood serum and not in the leucocytes."

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[203] Denys and Leclef: "La Cellule," T. xi, p. 198, 1895.
[204] Mennes: Zeit. f. Hyg., Bd. xxv, S. 413, 1897.
[205] Wright and Douglas: Proc. Royal Society, vol. lxxii, p. 357, 1903.
[206] Neufeld and Rimpau: Deutsche med. Woch., Bd. xxx, S. 1458, 1904.

This affords a first point in which opsonin corresponds with the thyro-parathyroid secretion: being stored in the red corpuscles it is secreted with the adrenoxidase to which it is linked, and thus becomes a constituent of the plasma.

Again, Bordet, as is well known, termed *substance sensibilisatrice* or "sensitizing substance" and Gruber *preparator* or "preparing substance" (Ehrlich's amboceptor) a body which rendered bacteria, red corpuscles, or any kind of cell in fact, vulnerable to the destructive action of Buchner's alexins (Ehrlich's complement). Now, in the first volume I emphasized repeatedly the fact that Ehrlich's complement—the identity and source of which he has so far failed to show—was the intra-leucocytic trypsin, *i.e.*, the proteolytic triad.

This affords three more facts which harmonize with my interpretation, and with experimentally established data concerning opsonins, since the "sensitizing" substance is shown to affect the bacteria; to do so without influencing the leucocytes; and finally, to prepare the bacteria for the phagocytic leucocytes.

A fifth confirmatory point is available in that, precisely as is the case with the *substance sensibilisatrice*, which, as I stated on page 735 in earlier editions, "stands, without undergoing alteration, heating up to 60° to 65° C.," Kinghorn and Twichell,[308] referring to the observations of Wright and Douglas, state that opsonins "lose their power when heated up to 60° to 65° C. for ten to fifteen minutes."

Again, Bordet, Buchner and Gruber do not refer to the fact that the "sensitizing substance" is a compound body; in my own allusions to its homologue, the oxidizing substance (now adrenoxidase) in the first volume, its heat limit is always given as 65° C. Now, opsonins have led to the same error: Potter, Ditman and Bradley[209] state that "Savtchenko[210] and Dean[211] regard certain opsonins and amboceptors as identical"—a seventh point in support of my interpretation.

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[307] Potter, Ditman and Bradley: Jour. Amer. Med. Assoc., Nov. 24, 1906.
[308] Kinghorn and Twichell: Amer. Jour. Med. Sci., Aug., 1906.

The same authors also write, however, "Hektoen[212] regards opsonins as distinct from amboceptors, and in proof of his opinion states that under certain circumstances normal serum may possess lytic, but not opsonic powers, and *vice versa;* again, that immunization may give rise to opsonic, but not to lytic substances; and further that heat may destroy the *opsonic* power without affecting the lytic amboceptors, and *vice versa.* Thus, while opsonin for anthrax bacilli, present in the serum of normal dogs, is destroyed by heating at 60° C. for thirty minutes, the amboceptor for anthrax bacilli present in the serum of normal dogs is not affected by heating at 65° for thirty minutes. Moreover, while the serum of white rats is normally anthracidal owing to the presence of a thermostabile substance that is inactivated by neutralization of the serum with oxalic acid, the same serum contains a thermostabile opsonin for anthrax bacilli which, however, is not inactivated by oxalic acid." The presence of two distinct substances is clearly shown in this quotation: (1) the substance destroyed at 60° and (2) the thermostabile substance. Now, as stated by Lazarus Barlow,[213] Metchnikoff holds that while the thermolabile body is confined in the phagocytes (his trypsic cytase), the plasma contains another, which is "thermostable, resisting a temperature of 100° C." We have seen repeatedly that the only substance in the plasma which is able to stand this temperature is adrenoxidase. On the whole, opsonin is not the amboceptor any more than it is adrenoxidase; it is a sensitizing ferment, destroyed at 60-65° C., *combined with adrenoxidase,* which is only destroyed at 100° or may even resist that temperature.

Under these conditions, however, adrenoxidase should contain the various components of the thyro-parathyroid secretion: we have seen that Gley found iodine in the red corpuscles; and the fact that this halogen is also found in practically all tissues shows that it must leave these cells with their adrenoxidase. The blood-platelets, as I have pointed out, are droplets of adrenoxidase: Schäfer[214] states that according to Löwit[215] they consist chiefly of a "*globulin,*" and that "as the result of microchemical work, Lilienfeld[216] considers that they consist of *nucleo-proteid.*" The two bodies being combined, the conclusions of both observers are justified. As we have seen that the main constituents of the thyroid secretion are iodine, nucleoproteid and a globulin (the others, xanthin, paraxanthin, etc., being wastes), the correspondence between the secreted products of the red corpuscles and the thyroid secretion are not only evident, but in the light of the facts submitted above, *these supposedly different bodies—originally derived from the thyro-parathyroids—and opsonin are one and the same substance.*

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[209] Potter, Ditman and Bradley: *Loc. cit.*
[210] Savtchenko: Ann. de l'Inst. Pasteur, T. xvi, p. 106, 1902.
[211] Dean: Proc. Royal Society, vol. lxxvi, p. 506, 1905.
[212] Hektoen: Jour. Amer. Med. Assoc., May 12, 1906.
[213] Lazarus Barlow: "Manual of Gen. Pathol.," p. 269, second edition, 1904.

This conclusion, which I reached in 1907, has been sustained by the experiments of Marbé[216a] which showed that thyroid extract increased the opsonins in animals.

Finally, Wright showed that vaccines increased the proportion of opsonin in the blood. Metchnikoff,[217] alluding to the experiment of Bordet in animals injected at various times with the blood of foreign species, remarks: "It is the sensitizing substance which appears in very great quantity as a result of these injections. von Dungern[218] has confirmed this observation, and has added the interesting fact that the *sensitizing substance* is found in great excess *in the serum* of the injected animals."

The influence of the thyro-parathyroid secretion or ferment on the anterior pituitary body now suggests itself; it is that produced on all cells. Referring to the pituitary, Böhm, Davidoff and Huber[219] state that "now and then alveoli containing a colloid substance, similar to that found in the alveoli of the thyroid gland, may be observed." Indeed, Schnitzler and Ewald[220] found in the pituitary body, "evidence of considerable iodine." This means, in the light of the evidence submitted, that the colloid substance is a combination of the secretory products of leucocytes (including any noxious substance they may contain) and the secretion of the red corpuscles, *i.e.*, adrenoxidase, including the thyro-parathyroid ferment with which it is combined. The surface of the test-organ is thus not only swept by the current of colloid which contains any noxious substance of which it must take cognizance, but it is simultaneously sensitized by the thyro-parathyroid secretion the colloid contains. Moreover, it is kept sensitive from another direction, viz., through the blood circulating in its sensory elements proper, since, as I have shown, adrenoxidase circulates in all nervous elements as well as in the perineural capillaries. As the thyro-parathyroid secretion is bound up with adrenoxidase, all nervous structures are kept sensitized by it, including the test-organ. The latter, unlike any other organ, is thus sensitized from two directions by a substance provided by the thyroid apparatus. Hence the morbid results observed when the latter's functions are impaired or annuled.

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[214] Schäfer: "T. B. of Physiol., vol. i, p. 154, 1898.
[215] Löwit: Arch. f. exper. Pathol. u. Pharmak., Bd. xxiv, S. 188, 1888.
[216] Lilienfeld: Arch. f. Physiol., S. 115, 1892.
[216a] Marbé: C. r. de la Société de Biologie, June 13 and 20, 1908.
[217] Metchnikoff: "L'Immunité dans les Maladies Infectieuses," 1901.
[218] von Dungern: Münch. med. Woch., Bd. xlvii, S. 677, 1900.
[219] Böhm, Davidoff and Huber: Loc. cit., p. 422.
[220] Schnitzler and Ewald: Wiener klin. Woch., July 16, 1896.

This involves the conclusion that the tissue and other living elements are also sensitized. Bordet's "substance sensibilisatrice" was found by him to sensitize all cells besides bacteria, even the red corpuscles themselves—as is shown indeed by their proneness to hæmolysis.

The test-organ destined by Nature to protect the whole organism against disease is thus kept attuned to the highest pitch to carry on its all-important mission. As the morphological homologue of the olfactory organ, it would, in keeping with the latter, fail to transmit impressions to the posterior pituitary and to awaken therein the secretory-motor stimuli to the adrenals through which cellular metabolism is sustained, were it not constantly stimulated. Cretinism and myxœdema occur when the test-organ is inadequately activated by the thyroparathyroid secretion; the organism lives, but much as does the plant; hence the term *"l'homme-plante"* attributed to cretins.

Yet, we have seen that even plants and ancestral animals utilize iodine. Here again, however, the accumulation of cell-colonies gradually as the higher forms were evolved, imposed the need of a greater supply of the iodine—or iodine-ferment, the compound of which the haloid is a component in all living structures: the delicate endostyle of the Tunicata and lower

Chordata (see *end* in the illustration on page 963) gradually developed therefore into the thyro-parathyroid apparatus, remaining throughout the entire phylogenetic scale closely related with the respiratory apparatus—the gill-bars in ancestral vertebrates—the lungs, as I have shown, in the higher vertebrates, including man.

Sensitiveness of the cellular elements thus assumes a cardinal rôle in the vital functions of all organisms. The reason for this imposes itself when the part that *irritability* plays in Nature is recalled: "Every process of stimulation requires two factors," writes Verworn,[221] "a stimulus and a body that is irritable. If the two factors come into correlation there results a phenomenon of stimulation, a reaction." The muscular contractility which will cause detached fragments of the heart muscle to continue beating is but a manifestation of this kind. This applies as well to the skeletal muscles in function. Here, "the irritability depends upon the fact that great quantities of potential energy are accumulated in the living substance of the muscle so that the introduction of only a small quantity is needed to transform it into actual energy." The potential energy is the true source of contraction in the muscular mass; but the relatively diminutive proportion of energy that the nerve impulse adds thereto suffices to provoke contraction. Nourished by leucocytic granules (endowed with life by the adrenal active principle) and kept free of wastes by the hydrolytic triads, the tissue-cell is eminently prepared to *assume* the sensitized state; but pending this event it is latent as a living entity; it lives but cannot work. Throughout Nature, bound up with the albumins and colloids of animals and plants, iodine (as I interpret its rôle) endows it with the capacity to react, *i.e.*, with the power to functionate under appropriate stimuli.

On the whole, the following conclusions appear warranted: (1) *the parathyroids supply a secretion which differs from that of the thyroid only that it is richer in iodine and far more active;* (2) *the secretions of the thyroid and the parathyroids being mixed before reaching the lungs, they constitute, physiologically, but one substance;*. (3) *the thyro-parathyroid secretion is a ferment-like compound of iodine, nucleo-proteid adren-*

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[221] Verworn: "General Physiology," Trans. by Lee, p. [illegible], 1899.

oxidase; (4) on reaching the pulmonary alveoli, it is absorbed by the red corpuscles along with adrenoxidase, becomes part of the latter, and is distributed with it to all parts of the organism, including the blood; (5) its physiological function is to sensitize all cells and cellular elements, physiological or pathogenic, whether in the tissues (including the nervous system) or in the blood (including its digestive leucocytes or phagocytes), and thus to render them vulnerable to the action of the hydrolytic triads or "ferments" they—the tissues, plasma and leucocytes—contain; (6) the nervous elements of the pituitary body, including those constituting the test-organ, being, like all other cellular elements, the seat of metabolic exchanges, they are likewise sensitized by the thyro-parathyroid secretion and their functional efficiency, i.e., the vigor with which they react to sensory impressions and initiate motor stimuli, is commensurate with the degree of sensibility thus conferred upon them; (7) when the test-organ is adequately sensitized, the intrinsic metabolism of its elements is sufficiently active to sustain the secretory activity of the adrenals, and therefore the vital process itself up to the normal physiological standard; (8) when, conversely, it is inadequately sensitized through deficiency or qualitative impairment of the thyro-parathyroid secretion, the adrenals are insufficiently stimulated to insure normal oxygenation, the vital process and therefore all functions are rendered correspondingly torpid—a condition which entails cretinism in the child and myxœdema in the adult.

Hereafter I will refer to the thyro-parathyroid secretion as *thyroiodase.*

THE INTERNAL SECRETIONS AS THE BODY'S AUTO-PROTECTIVE SUBSTANCES AND AS THE FOUNDATION OF RATIONAL THERAPEUTICS.

In his Herter Lecture at Johns Hopkins (1906), Sir A. E. Wright gave a résumé of his valuable researches and of those of his associates, Drs. Ross and Douglass, upon the rôle of the "opsonins." These were referred to as newly found substances which rendered various bacteria susceptible to the phagocytic action of the leucocytes. After dividing the immunizing constituents of the blood into opsonins, bactericidal (bacteria-kill-

ing), and *bacteriolytic (bacteria-dissolving)* substances, opsonins and agglutinins, and grouping them under the term "bacteriotropic substances," the lecturer referred to them as the natural immunizing constituents of the body. He had found, moreover, that when a given virus was injected into the blood, these bacteriotropic substances increased in amounts, in proportion, to a certain extent, with the quantity administered.

Three years ago, in an address before the Chelsea Clinical Society of London, Sir A. E. Wright[232] stated that *while their origin in the body was unknown*, "all the protective substances which were involved in the cure of disease were to be regarded as produced by internal secretion." Alluding to various disorders, including tuberculosis, in which "the blood was deficient in protective substances," he held that if they [pathologists, I presume] "knew the laws by which such substances were produced," we could "call forth a production of those substances" in the patient. In all of some thirty cases—boils, acne and sycosis—which he had treated by inoculations, "there had not been one of them in which there had not been produced enough of that internal secretion to enable the body to kill off the staphylococcus," while "patients with tuberculosis recovered if they produced enough of the internal secretion to render their bodies uninhabitable by the tubercle bacillus." He held, moreover, that "it should be recognized that chronic or local infection was a symptom of defective internal secretions, and that those secretions could be elaborated in the body when there was youth, strength and health, by the application of the appropriate stimulus given in proper quantities."

Now, a year earlier, I had pointed out in the first volume of the present work[233] and elswhere,[234] that the blood's immunizing bodies[235] were the internal secretions of the ductless glands and formulated the principle that "the power of the organism to antagonize the constitutional effects of pathogenic germs, their toxins and other poisons, is directly proportionate to the functional efficiency of the adrenal system," the latter being composed of the thyroid gland, the anterior pituitary and the adrenals. I laid stress, at the time, on the fact that[226] "all forms of vaccination endow the inoculated subject with enhanced activity of the adrenal system, and, therefore, of all structures which take part in the defense of the body" and ascribed the immunizing influence of Pasteur's method against hydrophobia, vaccination against small-pox, the effects of Coley's mixture of erysipelas and bacillus prodigiosus toxins in sarcoma, Koch's tuberculin, etc., to this process. I repeatedly emphasized the fact that the cure of disease should be considered as produced by internal secretions, that bacteria could not live where the immunizing substances were present in sufficient quantity, etc. That Dr. Wright's researches have confirmed my conclusions is self-evident.

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[232] Sir A. E. Wright: Brit. Med. Jour., Mar. 19, 1904.

[233] *Cf.* vol. i, pp. 600 to 606, 728 to 751, in the first three editions.

[234] Sajous: Monthly Cyclo. of Pract. Med., Jan., March., 1903; Phila. Med. Jour., Mar. 7, 1903.

[235] *Cf.* vol. i, p. 765, in the first three editions.

That he should be unable, however, to point to the source or identity of the immunizing bodies is but normal. Elsewhere[227] I had occasion to write: "Pathologists will continue to work in the dark, as they have now been doing several years, until they realize that the very few substances, to which various names have been given: Buchner's alexins, Ehrlich's complement, Metchnikoff's cytase, Ehrlich's intermediary body or amboceptor, Bordet's sensitized substance, etc., *are* internal secretions in the true sense of the word: *i.e.*, products of *ductless glands*." To this series, as shown in the preceding section, "opsonin" is also to be added.

What is, under these conditions, the nature of the immunizing substances that appear in the blood under the influence of toxins?

In the light of the evidence previously adduced, when a poison or toxin appears in the blood, a fraction of the poison will reach the pituitary body (with the plasma or with the leucocytes) and, if the dose be not excessive, it will excite the test-organ and provoke a protective reaction in the body at large. This reaction being produced through the adrenals, the first substance to appear in the blood is of course adrenoxidase. As this entails increased oxygenation of all organs, their secretory and formative activity is augmented; as a result of this, the pancreas produces more trypsinogen. The leucocytogenic organs create more leucocytes—mainly neutrophiles and eosinophiles. This double leucocytosis was noted by Muir,[228] who remarked, as a result of his observations, that "whether they act as direct phagocytes or indirectly, the eosinophiles evidently play an important part in the defense of the body." As I interpret the rôle of these cells: they migrate from the iodine reserves (the bone-marrow) to the thyroid and parathyroid glands, to hasten the formation of the sensitizing secretion of these glands. This secretion being taken up by the red corpuscles in the lungs, the blood-plasma receives the first of its "immunizing" substances, viz., adrenoxidase, bound up with the sensitizing thyro-parathyroid secretion. Now, this identical combination is a prominent factor in all the experimental work recorded by pathologists, as the following cursory review of this research will show.

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[226] *Cf.* vol. i, p. 765 *et seq.*, in the first three editions.

[227] Sajous: Monthly Cyclo. of Pract. Med., Apr., 1904.

Adrenoxidase plus sensitizing substance. Adrenoxidase, as we have repeatedly seen, is only destroyed at 100° C., while the second substance, opsonin, is, according to Wright and Ross, destroyed at from 60° to 65° C. Now, Metchnikoff,[229] as previously stated, refers to the presence of the thermostable 100° C. substance as "circulating in the blood-plasma" as Pfeiffer's "specific immune body." On the other hand, the latter, which has also been termed "amboceptor" by Ehrlich, "substance sensibilisatrice" by Bordet, "copula" by Metchnikoff, "desmon" by Müller, etc., is destroyed at 65° C. This paradoxical fact finds an explanation in the presence of two substances, adrenoxidase and the sensitizing substance, the more readily observed phenomena being carried on by the latter because of its destruction at the lower temperature.

Still, if this be true, both these bodies should originate from the red corpuscles: Metchnikoff clearly differentiates the 100° thermostable substance as a constituent of the plasma from other substances, referred to below, which originate from leucocytes. More clearly specified in this particular, however, is the source of the sensitizing substance or immune body. While Bordet and von Dungern[230] held that the red corpuscles excited the production of this substance, Nolf[231] showed that it was a product of these cells. The rôle of this substance is evidently that ascribed by myself to the thyro-parathyroid secretion and by Wright to the "opsonin," for, as stated by Wassermann,[232] according to Bordet, "the substance sensibilisatrice plays the rôle of mordant. It makes the blood-cells [and also bacteria, toxins, wastes, detritus, etc., I should add] vulnerable to the alexin, so that the latter can attack the cells and dissolve them."

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[228] Muir: Glasgow Med. Jour., Jan., 1905.

[229] Metchnikoff: Cited by Lazarus Barlow: *Loc. cit.*, p. 469.

[230] von Dungern: Münch. med. Woch., Bd. xlvi, S. 405, 1899; Bd. xlvii, S. 657, 962, 1900.

This brings us to the next stage of the defensive process:—

Phagocytosis, carried on by the intracellular digestive triad, trypsin. A multitude of neutrophiles are now present in the circulation ready to ingest and digest the sensitized bacteria, toxins, cells, wastes, etc.—Metchnikoff's phagocytes. We have seen repeatedly that they contain what I have termed the "digestive triad," viz., trypsinogen, nuclein, and adrenoxidase, which, combined, constitute the ferment trypsin. Charrin and Levaditi,[233] von Zaremba[234] and others have demonstrated the digestive activity of pancreatic juice on bacteria and toxins; Metchnikoff, Arthus, Mouton[235] and others found trypsin in leucocytes. Moreover, the labors of Bordet, Metchnikoff, Ehrlich and Morgenroth have demonstrated that the destruction of bacteria, etc., was due to the presence in the phagocyte of a digestive substance. "This substance, a sort of digestive ferment," writes M. Labbé,[236] "attacks and destroys the cells and bacteria that are sensitive to its action; thanks to it, pathogenic elements are destroyed within the leucocytes." As is well known, the efficiency of phagocytic protection is proportionate with the relative number and activity of the phagocytes present, and if these cells increase promptly in the blood, they soon dispose of the bacteria; conversely, if the latter are too numerous, or too virulent, the phagocytes are overwhelmed, partly by bacterial toxins, and general infection occurs. Phagocytes, therefore, owing to the digestive triad they contain, play a leading part in the defense of the body, in accord with Metchnikoff's doctrine.

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[231] Nolf: Ann. de l'Inst. Pasteur, vol. xiv, pp. 297, 492, 1900.
[232] Wassermann: "Immune Sera," Transl. by Bolduan, p. 5, 1904.
[233] Charrin and Levaditi: Semaine méd., Mar. 22, 1899.
[234] von Zaremba: Archiv f. Verdauungskrankheiten, Bd. vi, S. 466, 1900.
[235] Mouton: Ann. de l'Inst. Pasteur, T. xvi, p. 457, 1902.
[236] M. Labbé: "Le Sang," p. 44, Paris, 1903.

The third stage of the auto-protective process is now in order; the appearance in the blood of:—

The digestive triad as the bacteriolytic constituent of the plasma. While Pfeiffer, Fodor, Nuttall and others found that the blood-plasma possessed bactericidal properties, Buchner and Hankin isolated the active substance, and termed it "alexin." As stated above, this is the trypsic body, or digestive triad which destroys bacteria within the phagocytes. The experimental demonstration by Bordet, Metchnikoff and others that the phagocytic alexin was a trypic ferment is further sustained by Buchner's own labors (1899), which showed that there existed a close connection between the leucocytes and the presence of alexins in the plasma. Buchner showed, moreover, that alexins were derived from leucocytes, a conclusion sustained by the investigations of Bail, Schattenfroh and others, and now generally accepted. As to the manner in which alexins leave the leucocytes, Metchnikoff and Gengou have held that they were liberated by breaking up of the cell. We have seen, however, that this view can no longer hold. Indeed, Buchner showed that they were secreted by the cells, a conclusion sustained by Ehrlich's investigations and those of other observers. On the whole, it is evident that while leucocytes use their intracellular trypsin to digest the bacteria they ingest, and, as I have pointed out, convert them into nutrient granules which they carry to all tissue-cells; they can likewise secrete their digestive triad or trypsin with their granulations, into the plasma, thus endowing the latter with its bactericidal property. The interrelations of these various substances in the blood will be referred to in the next chapter.

From start to finish, therefore, it becomes possible to account for the auto-protective or "immunizing" process in disease by means of substances derived from the ductless glands: adrenoxidase, the thyro-parathyroid secretion, and the pancreatic internal secretion.[237] Even the phagocytes which utilize the latter are ductless glands, since they also secrete their bacteriolytic substance in the blood. Moreover, one salient fact has asserted itself, viz., that the intra-phagocytic and plasmatic bactericidal and antitoxic triad is the identical one which, as I have pointed out, fulfills the cardinal function in the vital process with the adrenal active principle as the chief factor. Here, again, the paramount influence of this principle prevails, since it is to its identity as the ferment of the bactericidal ferment, *i.e.*, as a catalytic, that it can protect the body whose life it serves to initiate and sustain.

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[237] *Cf.* this vol., p. 884.

Wright's subdivision of the "bacteriotropic substances" into bactericidal and bacteriolytic bodies, opsonins and agglutinins, may be reduced to three, under these conditions, since a pathogenic organism is necessarily killed by the trypsin whether in the phagocyte or in the blood-stream, as they are in the intestinal canal, viz., the digestive triad, trypsin, the thyro-parathyroid secretion, opsonin, and agglutinin.

We are left, however, with an unknown quantity: "agglutinin." What are the nature and mode of action—both unknown—of this substance?

As interpreted from my standpoint, agglutination is the initial phenomenon of bacteriolysis, and is also caused by the thyro-parathyroid secretion. It is a coincident phenomenon of, or succeeds the sensitization of pathogenic organisms or of any substance to be dissolved by the digestive triad in the plasma. Clumping and digestion of the red corpuscles—hæmolysis—are due to the same factors, these cells sharing the fate of the bacteria when the digestive activity of the plasma becomes excessive.

The landmarks of the thyro-parathyroid secretion are readily traced in the experimental history of agglutinin. Thus the temperature at which the latter is destroyed is the same. Wassermann,[323] for instance, writes: "The agglutinins are fairly resistant substances which withstand heat to 60° C., and lose their power only on heating to 65° C. It is possible, therefore, to make a serum hæmolytically inactive by heating to 55° C., and still preserve its agglutinating power." It is not to adrenoxidase alone that it is due, since the latter is only destroyed at 100° C.; nor can it be the digestive triad which is destroyed at 55-56° C. On the other hand, 60° to 65° corresponds with opsonin, which, as we have seen, is the parathyroid secretion. Its intimate functional relationship with adrenoxidase is also suggested by the fact that Baumgarten[239] was led experimentally to conclude that agglutinin and Ehrlich's complement (adrenoxidase) were identical, while Bordet and von Dungern held that hæmolysins might originate from the red corpuscles. Again, we have seen that it was in the lungs that the thyro-parathyroid secretion was taken by the plasma and red corpuscles: Deutsch found that the lungs of *non-immunised* guinea-pigs were the only organs which exceeded in agglutinating activity that of the blood-plasma, and therefore of all other body fluids.

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[323] Wassermann: *Loc. cit.*, p. 36.

The presence of agglutinin in plants suggests the active agent in the process. Ricin, obtained from the castor-bean, is very active in this particular, as are abrin, the phallin of mushrooms, and other plant albumoses. All plants containing more or less iodine, oxidases, and nuclein, as we have seen, the conditions therein are such as to permit the elaboration of an iodine-ferment (which may be very powerful, as in the plants mentioned) very similar, in its chemical properties, with those of the thyro-parathyroid secretion. This involves the conclusion, however, that iodine (the main active agent of the secretion and of the vegetable compound corresponding with it) should like ricin, abrin, etc., produce hæmolysis: "Iodine," writes Cushny,[240] "is said to dissolve the red blood-corpuscles when it is brought in contact with them outside the body, and to form a combination with hæmoglobin." The corpuscles themselves and the plasma in which they bathe affording the other constituents for the formation of an iodine ferment, the effect is the same as if an energetic blood hæmolysin had been used. Exception has been taken to Ehrlich's suggestion that the agglutinin of plant albumoses (phallin, ricin and abrin) was the same substance as hæmolysin; his view is perfectly warranted, however, since, as stated above, plants contain not only the iodine ferment, but also trypsin, etc., to follow up agglutination with digestion, *i.e.*, hæmolysis. Indeed, Baumgarten found that partial hæmolysis of the red corpuscles occurred after they had been agglutinated with ricin and abrin when the mixture was energetically shaken.

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[239] Baumgarten: Berl. klin. Woch., Bd. xxxviii, S. 1240, 1901.
[240] Cushny: "Pharmacol. and Therap." third edition, p. 519, 1903.

That agglutination is a precursor of hæmolysis is a recognized fact. Thus, Bordet[241] found that "agglutination of the red corpuscles occurs previous to their solution," that "the solvent power of the specific hæmolysins depended on the combined action of *two* constituents of the specific serum," and, moreover, that "when the fresh hæmolytic serum was warmed for half an hour at 55° C., it lost its power."* That both the amboceptor (adrenoxidase) and the complement (the digestive triad) are necessary for the production of hæmolysis has in fact been demonstrated by Ehrlich and Morgenroth.[242] All the more recent investigations have not only served to confirm these fundamental features of the problem, but they have sustained Ehrlich's view that hæmolysis is a fermentation process analogous to digestion. This applies as well to bacteriolysis, as is well known. Agglutinin stands out prominently as an independent substance in this connection, since it does not itself immunize. Durham[243] found that the presence of large quantities of agglutinins in the blood of animals did not prevent death from infection. It is plain, therefore, that agglutination is but an initial phenomenon of the immunizing process.

The identity of agglutinin as the thyro-parathyroid secretion thus asserts itself in various ways. The two bodies correspond: as to the temperature at which their action ceases, 60° to 65° C.; their source in the blood-stream, the lungs; the identity of their main active agent, iodine; their mode of distribution, the red corpuscles; and finally, their sensitizing property. Having shown in the preceding section that opsonin was also the thyro-parathyroid secretion, it is plain that opsonin and agglutinin likewise represent the one substance.

Returning to Wright's subdivision of the "bacteriotropic substances" of the blood into four bodies, it has become evident that we need only take two into account, viz., the thyro-parathyroid secretion (opsonin, agglutinin, substance sensibilisatrice) and the digestive triad (trypsin, cytase, alexin, complement, etc.). Adding thereto phagocytosis, we have the three active factors of the immunizing process which are brought into action when bacteria, *i.e.*, their toxins or endotoxins, or any other poison capable of exciting the test-organ of the pituitary body, enters the blood-stream.

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* The experiments of several investigators to determine the part taken by the red corpuscles in agglutination and hæmolysis are rendered valueless by the fact that, unlike Bordet, they failed to use fresh serum or exposed the latter or the corpuscles to contact with substances which annulled the activity of their secretion.—S.

[241] Bordet: Cited by Wassermann: *Loc. cit.*, p. 3.

[242] Ehrlich and Morgenroth: Berl. klin. Woch., Bd. xxxvii, S. 681, 1900.

[243] Durham: Brit. Med. Jour., Sept. 3, 1898.

In the first volume, over four years ago, I advanced the view that a poison or toxin capable of stimulating the adrenal center, *i.e.*, the test-organ, protected the organism by increasing the proportion of immunizing substances in the blood, and that various diseases developed because of the deficiency of such substances. Wright's researches have demonstrated that during infection by certain bacterial species, the proportion of "bacteriotropic substances" is below normal, the patient's blood being then in what he terms the "negative phase," while—and this is the most important result of his valuable researches—by means of bacterial vaccines, tuberculin, etc., judiciously employed as to quantity and intervals between the doses, the immunizing substances can be so increased in the blood that they exceed greatly the normal limits. This raises the patient's defensive powers to such a degree, *i.e.*, brings them up to the "positive phase," that the invading bacteria and toxins are more or less promptly destroyed.

Wright, however, found that great precautions were necessary. By what he terms the "opsonic index," *i.e.*, the average number of bacteria taken up by each leucocyte, he is able to gauge the proportion of bacteriotropic substances in the blood. He observed also that while inoculations cause the "bacteriotropic pressure" to rise, the latter tends constantly to return to normal. This imposes the need of regulating carefully the intervals between the doses in order to keep the bacteriotropic activity of the blood above normal—a fact which in itself imposes the need of frequently examining the blood. The use of large doses in no way tends to sustain the blood's immunizing power; experience has shown that these are dangerous, particularly in the negative phase, and that they may even cause death. Again, Wright[344] refers to what he terms another "serious aspect of the question" as follows: "Here is an inoculation after which the resisting power runs down; but after a time it rises and the patient is re-inoculated with a large dose; the resistance goes down further, and before he can recover another dose is given and the resistance goes down still further. So anybody can inoculate with successive doses and reduce the resisting power to anything he likes. It is quite easy by this method to reduce the resisting power of the blood enormously."

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[344] Wright: Canadian Practitioner and Rev., Nov., 1906.

In the first volume and elsewhere,[245] I laid stress on the importance of recognizing the two phases of action to which Wright refers. I wrote at the time that "the majority of drugs, toxins, physiological toxalbumins, etc., *stimulated* the adrenal system when the proportion of these agents in the blood did not exceed a certain limit, and that *when this limit was exceeded, i.e.*, when the dose administered, or the amount of toxins secreted by bacteria, etc., was excessive, it either *inhibited or arrested* the functions of this system." Briefly, the observations of Wright are clearly accounted for when the functions of the test-organ and the adrenals are taken into account: *Each toxin* or *drug* capable of exciting the test-organ can raise its functional activity *up to a certain limit;* beyond this it paralyzes its functions whether the dose administered be excessive or whether it be given in smaller doses too frequently, thus leading to cumulative action.

The result in both cases is either gradual or sudden adrenal insufficiency with its consequences: more or less rapid diminution of adrenal secretion, *i.e.*, of adrenoxidase. This means that the protective or immunizing substances, which are simultaneously the life-sustaining constituents of the body, are quantitatively inadequate. The auto-protective functions always working hand in hand with the vital processes, the general symptoms of poisoning invariably include, as I have already pointed out,[246] those that follow removal of the life-sustaining organs, the pituitary and the adrenals, viz., marked adynamia, hypothermia, lowered vascular pressure with weak and small pulse, dyspnœa, cyanosis and convulsions,—the number and violence of the symptoms depending upon the extent to which the functions of the test-organ are inhibited.

In the first volume[247] I wrote: "Artificial immunization means the introduction not of bacteria, but of their products: the toxins themselves. These do not reproduce any more than the alkaloids of plants reproduce; they act with more or less vigor upon the adrenal system, precisely as do these alkaloids or other drugs. Indeed, if, instead of 'toxins' they were called as are the alkaloids, 'medicines,' their use would inspire no more fear of complications than do the former, and their true position in therapeutics would be accorded them." But this refers to uncontaminated toxins. Are we sure that tuberculin, for instance, is always free of pathogenic, living, organisms? Karl von Ruck,[248] who can speak authoritatively in such matters, writes in this connection, after referring to the inconstancy of the results obtained with tuberculin R.: "Another danger from its use was soon shown to exist by Trudeau,[249] who found living, virulent tubercle bacilli in the preparation, after I had myself[250] directed the attention of the profession to the probability of such an occurrence."

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[245] Sajous: Phila. Med. Jour., Mar. 7, 1903.
[246] *Cf.* vol. i, p. 773, in the first three editions.
[247] *Cf.* vol. i, p. 764, in the first three editions.

Again the question of technique is an important one. The safeguards urged by Prof. Wright will surely be utilized by men who have acquired his skill, and insure comparative safety; but when we take into account the small proportion of such men among the hundreds of thousands of practitioners in civilized countries, and the fear of the great majority of medical men and their patients that the inoculation itself may prove a source of disease, it becomes plain that pending at least the disappearance of these untoward circumstances, our *armamentarium pharmacopœiæ* should remain our standby.

Summarizing the evidence and conclusions bearing upon the question I have so far submitted, the following conclusions seem warranted:—

(1) *Certain drugs, however introduced into the body, can, by stimulating the test-organ of the anterior pituitary, increase the bacteriolytic and antitoxic properties of the blood;* (2) *the immunizing agencies thus increased are* (*a*) *the thyro-parathyroid secretion, an iodine-ferment (now known as the sensitising substance, opsonin and agglutinin) which sensitizes and softens pathogenic organisms, preparing these, and probably all poison-*

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[248] Karl von Ruck: Med. Record, Jan. 20, 1906.
[249] Trudeau: Medical News, Aug. 28, 1897.
[250] Karl von Ruck: New Orleans Med. Jour., July, 1897.

ous or otherwise harmful substances, broken-down cells, wastes, etc., for ingestion and digestion by the phagocytes; (b) the phagocytes, which ingest the bacteria to digest them by means of their intracellular trypsin; (c) the trypsin secreted by phagocytes or other leucocytes into the blood-stream and which digests therein what bacteria, toxins, toxic wastes and other noxious substances are not destroyed by the phagocytes.

Concerning the poisonous effects: (3) *drugs which are capable of stimulating the test-organ and are therefore able to enhance the efficiency of the immunizing substances directly or indirectly, differ in no way in this particular from inoculations of bacterial cultures, tuberculin, etc., and can only excite the test-organ up to a certain degree, varying more or less with each drug;* (4) *when this limit is exceeded owing to the use of excessive doses or of small doses given in too rapid succession, poisoning occurs;* (5) *the earlier symptoms of poisoning are those of excessive activity of the drug used or of the chemical combinations it may form in the alimentary canal, the blood, the leucocytes, the subcutaneous tissues, etc;* (6) *sooner or later, according to the drug or poison, general symptoms appear which are common to all agents, drugs, toxins, etc., capable of stimulating the test-organ, viz., great weakness with flaccidity of the muscles, hypothermia, lowered vascular pressure, rapid and weak pulse, dyspnœa, swarthiness, cyanosis, convulsions (due to accumulation of toxic wastes) and coma;* (7) *these symptoms are due to diminution or cessation of tissue respiration, i.e., of general oxygenation, the result in turn of depression or cessation of the functions of the test-organ and of the thyro-parathyroid apparatus,*—owing to factors which are considered in succeeding chapters.

With Prof. Wright I fully concur when he contends[281] that "we have in the power of raising the antibacterial power of the blood with respect to any invading microbe, out of all comparison the most valuable asset in medicine." But I hold that we have, among the remedies that have been at our disposal many years, agents eminently capable of raising the bacteriolytic and antitoxic power of the immunizing constituents of the blood beyond even the limits required to antagonize any infection or any other form of toxæmia. Indeed, so intense is this action in the case of some of these agents that the blood-cells themselves are digested (hæmolysis) along with the bacteria. The practical experience accumulated by clinicians during the many years—centuries in some instances—that these agents have been employed, and the researches of therapeutists into their physiological action, have given us a working field which it will take decades of steady labor upon all questions relating to the use of tuberculin or other bacterial products by inoculation even to approach. We need not, therefore, deprive the present generation of the advantages that the magnificent lore of our profession affords. Within our reach are weapons whose every part is known to all and which, in power to destroy the greatest enemies of mankind, are second to none—provided their present empirical use give way to their scientific use, viz., with the test-organ of the pituitary and the organs which it controls as the foundation of the body's auto-protective resources. This binds indissolubly pharmacotherapeutics to the general principle of immunity—precisely the field I opened in the first volume of this work. We must learn to bow to Nature's powers; had her mode of work—the doctrine of Hippocrates—inspired all researches since his time, Medicine would not only rank as a Science to-day, but it would exceed all other sciences in perfection.

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[281] Wright: Cited by C. P. Aaron: N. Y. Med. Jour., Dec. 1, 1906.

As a final conclusion of this chapter, I would submit, therefore, that *immunizing medication is the foundation of rational therapeutics.*

CHAPTER XVIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS

THE PRESENT STATUS OF THERAPEUTICS.

In a Presidential Address[1] A. H. Bampton said already in 1907: "Scepticism is in the air. Even in this society, if any daring member has introduced a subject bearing on medical treatment, it has been with an apologetic air and humble mien, well knowing that if his remarks had any reference to the utility of drugs in the treatment of disease they would be subjected to good-humored banter, and received by those sitting in the seat of the scornful with amused incredulity." That the same spirit reigns on this side of the ocean hardly needs to be emphasized. But few years had elapsed since Frank Billings, also in a Presidential Address,[2] declared that "drugs, with the exception of quinine in malaria and mercury in syphilis, are valueless as cures," and what has been termed Osler's "black, hopeless, helpless, therapeutic pessimism," is quite as applicable to a large proportion of the medical men of our country. The present work, in fact, was begun under the influence of a very similar state of mind. It would be unfair, however, to incriminate only pharmacological knowledge on this score; pathology is quite as invalid when the relations of cause to effect are scrutinized. Indeed, Lewellys F. Barker's previously quoted estimate that "drugs of *unknown physiological action* cannot conscientiously be set to act upon bodily tissue *in disease in which we are ignorant of deviations from the normal,"* exemplifies succinctly the dual cause of the ignominious position in which practical medicine finds itself.

In 1920 also in a Presidential Address (American Therapeutic Society) I had to deplore the fact that our schools were increasingly neglecting therapeutics, and to show that it was because the functions of the ductless glands were overlooked, that a rational treatment of disease could not be attained.

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[1] A. H. Bampton: Leeds and West Riding Medico-Chirurgical Soc., Lancet, Jan. 19, 1907.

[2] Billings: 54th Annual Session of the Amer. Med. Assoc., 1903.

Referring only for the time-being to therapeutics, no apology is needed, therefore, if the interpretations of the physiological action of drugs I present herein differ totally from any yet advanced. The introduction of a series of functions besides, even, those of the adrenal system, viz., the various processes carried on by the anterior and posterior pituitary bodies and by the different leucocytes, the additional rôle attributed to the red corpuscles, the several blood constituents which play so important a part in the life process itself and the defence of the organism, etc., normally entails a complete transformation of the prevailing conceptions.

Our fund of experimental and clinical facts has not in the least been set aside. Indeed, experimental therapeutists have contributed a vast array of positive data which, utilized individually, *i.e.*, irrespective of any interpretation formulated by the investigators themselves, and suitably grouped, afford a rich source of material for the elaboration of doctrines based only on established facts, and, therefore, poised on a sound foundation. It is to Horatio C. Wood that we owe mainly this mode of investigation, and if it has not as yet borne substantial fruit, it is not owing to the fact that the principle is unsound, but because the building materials were incomplete. Besides the various organs enumerated above, are others, the functions of which have also been overlooked, Ludwig and Cyon's depressor nerve, for instance, discovered by these physiologists in 1866. As I will show below, this nerve plays an important part in the self-defence of the organism against disease. Again, the fact that the majority of the body-functions have remained unexplained by physiologists has rendered it impossible to understand many phenomena provoked by drugs. The manner in which a motor nerve produces its effects, for instance, is as obscure to-day as it was fifty years ago. Vasodilation is a prominent feature of the action of drugs, and yet the manner in which it is brought about is absolutely unknown. As pointed out under the next heading, this problem is readily solved when the presence of adrenoxidase in the blood-stream is taken into account.

Again, the accumulated evidence of all the practitioners of christendom for centuries is certainly of some value. As

Bampton states: "Although our treatment then, as now in part, may be stigmatized *empirical*, it was none the less founded upon careful clinical experience." Here also we have a vast array of solid data for the elucidation of the relations between cause and effect, *i.e.*, of the manner in which the organism responds to exogenous influences. Unfortunately, the laboratory experimenter is too prone to ignore the teachings of clinical experience, forgetting that, judged as an experiment, the use of a remedy in a given case is at least as elucidative, with the refined methods of investigation now at the disposal of the clinician, as his own. Were he to add this fund of information to his own resources, and scrutinize as closely as the protocol of his experiments the recorded results of the administration of the corresponding remedy in disease, he would soon withdraw therapeutics from the position into which it has undeservedly fallen, and raise it to the dignity of a science.

In the various familiar drugs studied in the following chapters, I have availed myself—as far as space would permit—of these two great sources of information; besides the functions of the organs I have introduced into the various problems. That this plan must be fruitful, is suggested by an important result reached, viz., that *in the case of each drug* the physiological action I submit, though differing totally from that now taught, *explains clearly how the disease or morbid symptom for which it is used is antagonized and overcome.* This, in itself, affords strong testimony to the effect that the new conception of pharmacodynamics I submit is, in its general lines, poised on a solid foundation.

Before study of the various agents considered in this chapter can be undertaken, however, the manner in which the vasodilator and depressor nerves produce their effects requires attention.

THE MECHANISM OF VASODILATION AND ITS RELATIONS TO ORGANIC FUNCTION.

The existence of vasoconstrictor nerves discovered by Claude Bernard in 1851, confirmed by Brown-Séquard the following year, has become one of the keystones of modern physiology, and its solidity has never been shaken. The mode of action of vasoconstrictors is also established. We cannot say the same, however, of the vasodilators; the actual existence of a dilator center, or even of true vasodilator nerves, in fact, is still undetermined.

In his summary of vasomotor actions, Foster,[3] for instance, says that "there is no adequate evidence that these vasodilator fibers serve as channels for tonic dilating impulses or influences." Landois and Stirling,[4] referring to the "vasodilator center" in the medulla, state that "its existence there has been surmised," and furthermore, that "the existence of vasodilator nerves is assumed." In another edition of the same text-book[5] published eighteen years later (1905), this is modified to the statement that, "although a center for vasodilator or vessel-relaxing nerves has not yet been demonstrated, the existence of such a center in the medulla may nevertheless be suspected." J. G. Curtis[6] states that "it is not known whether a vasodilator center is present in the bulb." The actual state of the question is aptly summarized by H. C. Chapman,[7] when he says: "Though numerous explanations have been offered of the manner in which the vasodilator nerves act, it must be admitted that none of them are satisfactory, and that it is not yet understood how their stimulation causes dilatation of the blood-vessels."

Even the stronger lines of testimony, those based on cutaneous hyperæmia, blushing, etc., in favor of the presence of vasodilator nerves in the spinal cord, including that afforded by excitation of the upper segment of the cervical sympathetic, after section, cannot stand close scrutiny. "Flushing of the skin, or a rise of temperature in it," writes Langley,[8] "are at times and in certain circumstances, produced by stimulation of the sympthetic; and it is generally believed that the changes are due to the presence of vasodilators. The evidence, on the whole, is in favor of the presence of such nerve-fibers, but it is I think, premature to regard the question as settled." The weakness of the whole scheme hardly needs to be further emphasized. When we consider that vasodilation is *the all-important factor of function in all organs,* the need of ascertaining the nature of this process imposes itself.

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[3] Foster: "T. B. of Physiol.," sixth American edition, p. [illegible], [illegible].
[4] Landois and Stirling: "T. B. of Physiol.," vol. ii, p. [illegible], [illegible].
[5] Landois: "T. B. of Human Physiology," tenth edition, p. 771, 1905.
[6] J. G. Curtis: "Amer. T. B. of Physiol.," vol. i, p. [illegible], [illegible].
[7] H. C. Chapman: "Treatise on Human Physiology," second edition, p. [illegible], [illegible].
[8] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. [illegible].

No one, of course, denies that dilator *effects* are witnessed in various organs; the obscure feature of the question is the *manner* in which these effects are brought about. Even Claude Bernard's memorable experiment, which conclusively demonstrated the existence of nerves capable of causing vasodilation, has remained unexplained, as far as the mode of action of the chorda tympani is concerned. The fact that division of the sympathetic (constrictor) fibers distributed to the submaxillary gland's vessels is followed by dilation of the latter and an increased outflow of blood led Bernard to suggest that the chorda tympani inhibited the sympathetic fibers. Granting that it does represent a physiological function, this interpretation fails to harmonize with several established facts. Among these is the observation of Schiff (1856) and confirmed by several investigators since, that "the vessels of any organ are dilated to a greater degree by excitation of the vasodilators than they are by paralysis of the vasoconstrictors."[9] It is evident that "inhibition" or "paralysis" should simply counteract the constrictor effects, the vessels retaining their normal diameter. In reality, the dilation is much more marked under excitation, and the submaxillary gland is no exception to the rule. Langley,[10] in discussing the mode of action of inhibitory fibers, refers to this view as untenable, and, alluding to "the bucco-facial region of the dog, the inhibitory fibers of the heart and the inhibitory fibers of the stomach and intestine," remarks: "We may conclude for all cases that the inhibition which we are considering is not produced by a lowering of the activity of sympathetic or similar nerve cells." Foster's[11] estimate in this connection is conclusive: "We may, if we please, speak of an 'inhibitory mechanism' placed in the heart itself," says this investigator, "but we have no exact knowledge of the nature of such a mechanism."

In the vasodilator phenomenon discovered by Claude Bernard we have an illustration of the *active* functions of all organs. But *how* does the chorda tympani cause vasodilation? The solution of this problem furnishes that of a multitude of questions in the domains of physiology, pathology, and therapeutics.

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[9] Schiff: Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 125.
[10] Langley: *Ibid.*, vol. ii, p. 672.
[11] Foster: *Loc. cit.*, p. 287.

If the foregoing estimates are reduced to their simplest expression, our knowledge of the source and nature of vasodilator impulses is about as follows: we have a *problematic* center, grafted upon another center known to transmit impulses of an *opposite* kind; this problematic center is *supposed* to be the source of dilator impulses through nerves which have *not* been shown to act as channels for them, and which serve to dilate vessels which do so *automatically*, when all nerves distributed to them are severed. In other words, the conception is illogical from start to finish. It may be objected that the cord itself is the source of dilator impulses, and that nervi erigentes, for instance, may be made to produce dilator phenomena reflexly when the cord is severed above the lumbar region. But this in no way modifies the situation, for the spinal centers are thus merely brought into line with others credited with similar functions: the pontine nucleus of the facial nerve, the source of the chorda tympani's stimuli, for example. The manner in which these spinal centers cause vasodilation is no less obscure.

A key to the situation is within reach if all prevailing theories are set aside and *facts* only are accepted as guides. We *know* that constrictor impulses originate from a vasomotor center or subsidiary centers; we *know* that vasodilator effects are produced. Why should *constrictor* impulses not give rise to *dilator effects?*

Claude Bernard's experiment is outlined by Leonard Hill[12] in the following words: "Exposing the submaxillary gland, he opened one of the efferent veins and observed the outflow of blood. On dividing the cervical sympathetic nerve, the blood flowed in increased volume and became more arterial in color. On exciting the same nerve the outflow entirely ceased and the gland became pale in color. He next excited the chorda tympani nerve; the gland blushed red, and almost immediately bright arterial blood gushed out from the vein. The vascular dilatation was, in this case, so great that the blood, with each pulsation of the artery, flowed from the veins in jets."

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[12] Leonard Hill: *Loc. cit.*, p. 122.

The chorda tympani fulfills a dual rôle. "When the chorda is stimulated," says Foster,[13] "there pass down the nerve, *in addition* to impulses affecting the blood-supply, impulses affecting directly the protoplasm of the secreting cells, and calling it into action." These fibers were traced to the secretory elements by Pflüger, and his observation was confirmed by Paladino in 1876, and subsequently by Navalichin and Kytmanoff, Fusari and Panasci, and Ramon y Cajal.[14] When, however, the fibers to the secretory cells are paralyzed, the vascular phenomena are not modified. "If a small quantity of atropine be injected into the veins," says Foster,[15] "stimulation of the chorda produces no secretion of saliva at all, though the *dilatation* of the blood-vessels takes place *as usual;* in spite of the greatly increased blood-supply."* This is a familiar physiological fact, first observed by Ludwig many years ago, which shows that however produced, the vasodilator effects must be ascribed to the chorda tympani only.

The salient features of Bernard's experiment, besides the vascular dilation, are an increased volume of blood, the presence of arterial blood, and the expulsion of the latter in jets coinciding with arterial pulsations. To meet the needs of the first of these phenomena, it is, of course, necessary (1) that an increased volume of blood be *admitted* to the organ, and (2) that the blood-pressure be increased behind the column of blood so admitted. Obvious as these two conditions are, however, they embody, it seems to me, a solution of the question in point, for: given an adequate pressure *behind* an increased *volume* of blood, we have a column which exerts centrifugal pressure upon the walls of the vessels through which it passes and capable, therefore, of *dilating* them. To account for the arterial character of this column of blood and its expulsion in jets, we require larger vessels than the arteriole in the gland proper. The three or four submaxillary branches which supply the gland furnish enough blood when the organ is inactive to form "a thin slow stream" and supply the needs of the mechanism. Derived as they are from the facial artery, any increase of their caliber would normally give free sway to the marked back pressure which this vessel affords. The close proximity of the facial artery to the external carotid, of which it is a branch, its anatomical relations with the submaxillary gland, and the fact that it pulsates actively, clearly point to this vessel as a prominent factor of the process. But how is it made suddenly to shift, as it were, an additional volume of blood into its submaxillary branches—which requires widening of the lumens through which the blood enters the latter—and simultaneously increase its own propulsive power? This increase must be very marked, for "during stimulation," says Foster, "the blood rushes out in rapid, full stream." A very simple mechanism, the various parts of which are familiar anatomical landmarks, seems to me to satisfy all the needs of the function.

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* The italics are my own.—S.

[13] Foster: *Loc. cit.*, p. 265.

[14] Ramon y Cajal: Testut: "Traité d'Anatomie Humaine," third edition, vol. iii, p. 175, 1895.

[15] Foster: *Loc. cit.*, p. 264.

We have seen that the chorda tympani alone increases the functional activity of the gland. This nerve has two sets of fibers: secretory and vasodilator. Both of these are given off (anatomically) from a small ganglion, the submaxillary, found above the hilum of the organ. A feature of the distribution of this ganglion's fibers, however, is that some of them penetrate the gland proper, while others pass directly to the walls of the submaxillary branches of the facial artery, and to the latter likewise. Now, all these vessels are within the limits of those supplied with vasa vasorum, at least that first given by Henle, 1.1 millimeter. Their walls thus receive blood as do other structures, and are also oxygenated directly from the general circulation. These nutrient arteries, the largest of which, according to Gimbert,[16] have a diameter of 0.017 millimeter, form an anastomosing network in the tunica adventitia, composed chiefly of fibrous connective tissue intermixed with a network of elastic fibers, but Kölliker, Eberth,[17] Aeby[18] and others since found that the outer third of the middle coat, which contains a large proportion of muscular cells disposed mainly in

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[16] Gimbert: Jour. de l'anat. et de physiol., T. ii, p. 630, 1865.
[17] Eberth: Stricker's "Handbuch," S. 192, 1869.
[18] Aeby: "Der Bau d. menschl. Körpers," S. 782, 1871.

Fig. 1.

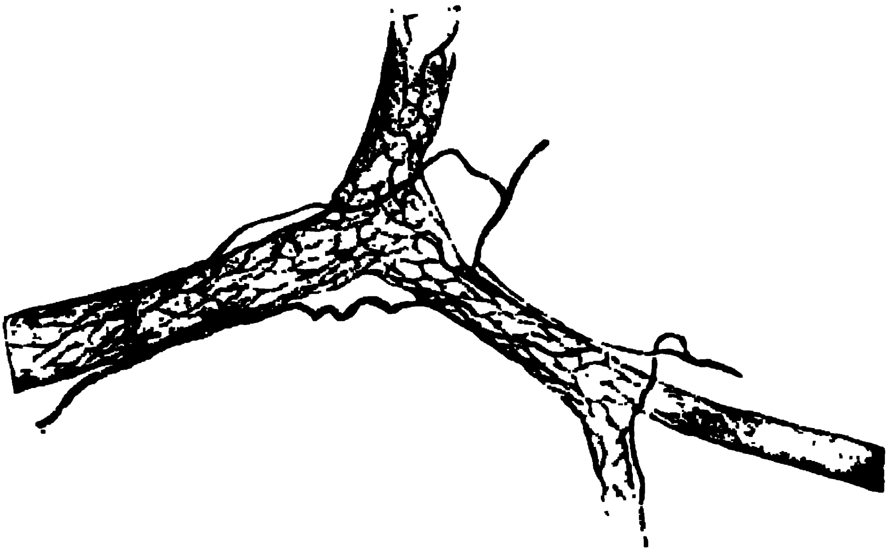
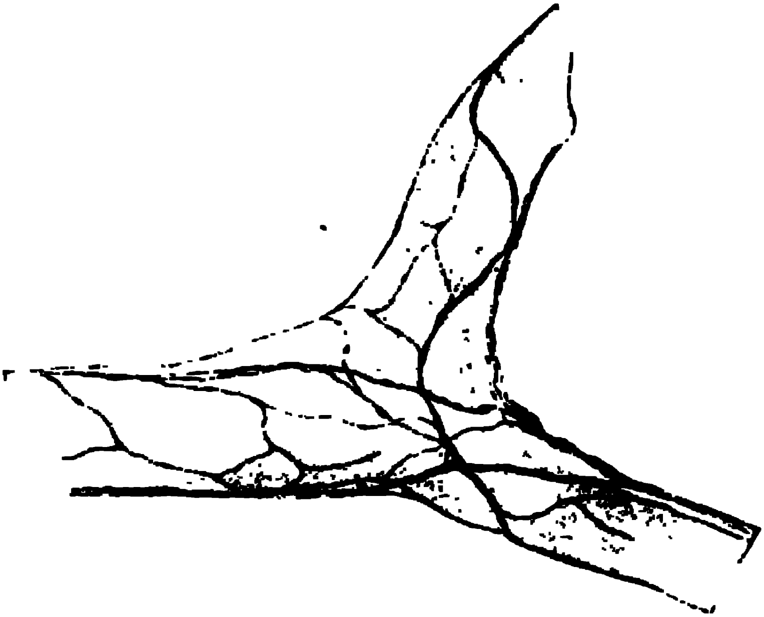


Fig. 2.



VASO-CONSTRICTOR NETWORKS AROUND ARTERIOLES. *[Joris.]*

Fig. 1, Arteriole of 280 microns × 55.
Fig. 2, Arteriole of 45 microns × 520.

a circular [illegible] was also provided with them. As shown by Ranvier,[19] vascularization of this coat, however, is an accompaniment of local pathological processes, and it is now generally thought that nutrient vessels do not penetrate this coat, except in the largest vessels. Shakespeare[20] says in this connection: "In the large vessels the middle and outer coats are supplied with blood-vessels—the vasa vasorum. In a few instances capillaries enter the tunica intima." While, therefore, vasa vasorum form an irregular but close meshwork in the fibro-elastic layer, they can only be said to reach in man the *surface* of the deeper or muscular layer.

That this network of nutrient capillaries is not itself supplied with vasomotor nerves is self-evident. These are doubtless distributed to the arterioles from which the capillaries are given off. That very minute arterioles are supplied with a vasomotor network is well shown in the annexed plate by Joris,[21] the upper vessel being about one-quarter of a millimeter, while the lower is but forty-five thousandths of a millimeter in diameter.

Important in this connection is the structure of the small vessels which, though referred to generally as "arteries," are, in reality, *arterioles* as regards histological structure and size. In this class of vessels, the internal coat is composed of endothelial plates only. Overlying this coat is one composed of what Ranvier termed the "internal elastic lamina," and of a layer of nonstriated muscular cells. Both this layer and the elastic layer are thus blended functionally, as it were. Now, if a cross section of such a vessel is examined, the elastic coat will be seen to have a wavy or festooned circular outline. "The internal elastic layer," says Ranvier,[22] "as are all structures composed of elastic material, are elastic only to a limited extent, and when it is compressed by the annular muscular layer, it often happens that the lower limit of elasticity is surpassed, and that in order to accommodate itself within the restricted space reserved for it, it must fall into longitudinal folds. Hence the festoon seen in cross sections, whereas in longitudinal sections of small arteries the folds formed under the influence of the muscular contraction cause it to appear as longitudinal striæ."

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[19] Ranvier: "Traité technique d'histologie," 1875.
[20] Shakespeare: Allen's "Anatomy," p. 72, 1884.
[21] Joris: Bull. de l'Acad. Roy. de Méd. de Belg., T. xx, p. 568, 1906.
[22] Ranvier: *Ibid.*

The manner in which the muscular coat of arterioles (meaning thereby the smallest of arteries, those which join the capillaries or the so-called pre-capillary vessels) is disposed around *them is also of considerable importance.* Thus, referring to these particular vessels, Berdal[23] writes: "The muscular cells form a single and continuous layer around the small arterial vessel. They are rolled spirally around the arteriole." As I will show in the next chapter, this enables these vessels (under the influence of sympathetic impulses) to propel their blood into the capillary system and to cause the arterioles to resume their normal diameter after they have been caused to dilate through the mechanism now in question.

The mechanical process of vasodilation will now appear. As nutrient arteries, the vasa vasorum supply the walls of the vessels to which they are distributed with blood obtained from a neighboring artery. This blood, as elsewhere, enhances the functional activity of these tissues by increasing metabolism in the cellular elements of which they are composed. Again, Roy[24] showed that the thermo-elastic properties of animal tissues differed from that of most other substances, and that they contracted when the temperature was raised and expanded when the temperature was lowered. We thus have two interdependent factors, one chemical and the other physical, dependent upon *the blood of the vasa vasorum,* capable of influencing the caliber of the vessels to which they are distributed. It is now evident that constriction of the vasa vasorum, by arresting or reducing the flow of blood to the walls of the vessels they nourish, will lower both metabolism and heat in these vessels, thus causing relaxation of their spiral muscular elements, and as a normal consequence, dilation. We thus have *vasodilation* of arteries and veins produced by *vasoconstriction* of their nutrient vessels—as illustrated in the next chapter.

This interpretation meets the—so far unexplained—fact that, as observed by Schiff, vessels dilated by their vasodilators expand to a greater degree than when their constrictors are severed. In the latter case, nerve impulses are alone arrested, and the vessel continuing to receive its nutrient blood, it soon resumes its normal caliber. When the nutrient blood of the vasa vasorum, on the other hand, cannot reach the vascular walls, *both* causes of constriction fail, since the walls are no longer able to respond to nervous stimulation. Again, it accounts for all the phenomena observed by Claude Bernard. The dilation of the gland's vessels is left, to a certain extent, under the influence of the volume of blood forced through them from behind. Here the source of general supply being the facial, a branch of the external carotid, we have not only—after vasodilation of the submaxillary arteries induced by constriction of their nutrient vessels—a marked increase of the volume of blood in transit through the organ, but it is propelled with such rapidity through the latter that the change to venous blood cannot occur. Finally, the streams, under the influence of the greater artery's periodical contractions, leave the gland in jets.

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[23] Berdal: "Histologie Normale," fourth edition, p. 307, 1894.
[24] Roy: Jour. of Physiol., vol. iii, p. 125, 1880.

Again, it does away with the need of a dilator center which no one has ever located, and of dilator nerves which no one has ever seen. Inasmuch, however, as Langley[25] found that extirpation of the superior cervical ganglion, which causes degeneration of the sympathetic fibers distributed to the vessels of the gland, did not prevent vasodilation when the chorda was stimulated, the constrictor fibers of the vasa vasorum are not sympathetic fibers. They are evidently the fibers in *cranial* nerves which *incite* functional activity in all organs by increasing the volume of their blood supply. In view of the fact that they provoke *dilator* effects by transmitting *constrictor* impulses, I will henceforth refer to them as "*stricto-dilator*" nerves—a distinction of paramount importance in therapeutics, as will be shown.

Finally, it meets all the conditions which, according to modern physiologists, an explanation of the mechanism of vasodilation should embody. Thus Howell[26] (1905) writes: "There has been much discussion in physiology as to the nature of the action of the dilator fibers. The muscular coat of the small arteries runs transversely to the length of the vessel, and it is plain that when stimulated to greater contraction through the constrictor fibers it must cause a narrowing of the artery. It is not so evident how the nerve impulses carried by the dilator fibers bring about a widening of the artery. At one time peripheral sympathetic ganglia in the neighborhood of the arteries were used to aid in the explanation, but, since histological evidence of the existence of such ganglia is lacking, the view that seems to meet with most favor at present is as follows: *the dilator fibers end presumably* in the muscle of *the walls of the arteries,* and when stimulated their impulses *inhibit the tonic contraction of this musculature and thus indirectly bring about a relaxation.* Dilatation caused by a vasodilator nerve fiber always presupposes therefore a previous condition of tonic contraction in the walls of the artery, this tonic condition being produced either by the action of vasoconstrictor fibers, or possibly by the intrinsic properties of the muscle itself."

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[25] Langley: *Ibid.*, vol. vi, p. 87, 1885.
[26] Howell: "T. B. of Physiol.," p. 545, 1905.

I conclude, therefore, that (1) *vasodilation is due, in the case of arteries and veins, to the diminution of blood-plasma and, therefore, of adrenoxidase, in the muscular layer of these vessels;* (2) *the blood-plasma being supplied to the vascular walls by the vasa vasorum, it is through contraction of these nutrient vessels that dilation of the vessels is caused;* (3) *the vasa vasorum receiving their blood-plasma from larger arterial vessels supplied with vasoconstrictor nerves, it is through vasoconstriction of these vessels that the volume of blood circulating through the vasa vasorum is diminished;* (4) *it is therefore by vasoconstrictor action that vasodilation is produced, "vasodilator nerves" having no existence in fact;* (5) *vasodilation being caused by constriction of the nutrient arteries of a vessel, the vasomotor nerves supplied to these nutrient vessels should not be termed "vasodilators" but "stricto-dilators."*

As Stewart[27] states, the fact that "an organ *in action* in general receives more blood than the same organ in repose" is "a physiological law of wide application." In the light of the evidence adduced, this constitutes the cardinal feature of all functional processes since it is to the presence of adrenoxidase in increased quantities that any exacerbation of activity, whether it be contraction or secretion, is due. It is apparent, therefore, that *this mechanism of vasodilation is that through which all exacerbations of activity in any organ, whether belonging to the alimentary, circulatory, locomotor, visual, auditory, or any other system, is incited and sustained.*

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[27] Stewart: "Manual of Physiol.," fourth edition, p. 225, 1900.

The influence of this mechanism will become evident under the next heading.

THE POSTERIOR PITUITARY THE SEAT OF A CENTER (THE ADRENO-THYROID CENTER) THROUGH WHICH THE TEST-ORGAN INFLUENCES THE SECRETORY ACTIVITY OF THE ADRENALS AND THYROID APPARATUS.

Leonard Hill,[28] in a review of our knowledge upon the mechanism of the circulation, writes: "In the rabbit, from the junction of the vagus and superior laryngeal nerves, there arises by two roots a fine nerve, which courses down the neck. On excitation of the *central* end of this nerve, Ludwig and Cyon witnessed a surprising fall of arterial pressure, accompanied by a slight decrease in cardiac frequency. The peripheral end failed to give any response to stimulation. Thus the purely afferent nature of the nerve was established." . . . . . "This nerve was named, by Ludwig and Cyon [in 1866], the depressor, for it possessed the power of depressing the arterial tension by 30 to 50 per cent. Ludwig and Cyon observed that, on stimulating the depressor, the kidney flushed red with blood, while the fall of arterial tension became insignificant after section of the splanchnic nerves." . . . . . "In different mammals, many variations are to be marked in the course of this nerve, but fibers with a depressor function are to be found." . . . . . "In man the homologous nerve arises from the vagus from the junction of the vagus and superior laryngeal nerves, but quickly joins again the main trunk of the vagus." . . . . . "Almost all parts of the vascular system can be thrown into dilatation by the depressor nerve."

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[28] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. II, p. 50, 1900.

The manner in which this effect is produced is still obscure: "The question is one not definitely settled," according to Hill, "and no conclusion as to the exact method of action of this nerve can be drawn." That it is not due to excitation of what he terms a "hypothetical vasodilator center" is suggested by the fact that vasodilator nerves "are easily exhausted by artificial stimulation," while the depressor is "inexhaustible." Cyon himself denies any relationship with such a center. As I have pointed out, moreover, the latter is not required to explain vasodilator phenomena. In fact, the spinal system cannot transmit the vasodilator impulses reflexly, since, as stated by Hill, after "dividing the spinal cord in the dorsal region, excitation of the depressor still causes a fall of arterial pressure." This obviously eliminates the vasomotor center also. Indeed, Porter and Beyer,[29] in an experimental study of this feature of the problem, state that they found "no evidence to warrant the opinion that the depressor nerves have special connections with the cells in the vasomotor center associated with the splanchnic fibers." Now, since as stated by Hill, "the splanchnic area is by far the most important seat of dilatation provoked by the depressor nerves," it is evident that the vasomotor center has nothing to do with the process. This leaves the latter totally unexplained.

This result is not surprising, in view of the fact that the functions of the pituitary body and of the thyroid gland, as I have interpreted them, alone make it possible to understand the process through which the depressor produces vasodilation. A comprehensive study of the question, which can only be represented here by a few salient facts, has led me to conclude that the depressor nerve produced this phenomenon by inhibiting the functions of the thyroid gland and pituitary body, and through the latter that of the adrenals.

Laulanié[30] states that the *pituitary body* "is in relation with the sympathetic, the vagus, and the depressor nerve"—a fact established by Cyon's experiments. That fibers of the cervical sympathetic are distributed to the pituitary body through the carotid plexus is well known. We have seen, moreover, that disorders of the anterior pituitary accompanied by local congestion give rise to glycosuria.[31] Now Cyon and Aladoff[32] found that lesions or removal of the upper thoracic or inferior cervical ganglia, or division of the loop of Vieussens, caused diabetes. All these contain sympathetic fibers which ascend to the superior cervical ganglion. Pavy[33] also states that "of all the operations on the sympathetic of the dog that have as yet been performed, removal of the superior cervical ganglion the most rapidly and strongly produces diabetes." As the fibers of the upper portion of the sympathetic other than those distributed to the pituitary supply various structures of the eye, those to the pituitary can alone explain this phenomenon. The manner in which this procedure causes diabetes is plain under these conditions: the sympathetic terminals to the pituitary being, as elsewhere, vasomotor, division of the nerve causes passive dilation of the vessels distributed to this organ, and the resulting congestion of the anterior lobe (by far the larger of the two, and the seat of the test-organ) gives rise to glycosuria by stimulating the adrenals. As previously stated, Blum, Croftan, Herter and others found that adrenal extract, adrenalin, etc., caused glycosuria.

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[29] Porter and Beyer: Amer. Jour. of Physiol., vol. iii, p. 23, 1900.

[30] Laulanié: "Eléments de Physiologie," second edition, p. [illegible], 1905.

Judging from the fact that vasodilation thus produced elsewhere in the body is temporary, however, the glycosuria should likewise be ephemeral: Pavy especially mentions the "temporary nature" of the marked diabetes following the experimental operation. On the other hand, if division of a nerve causes vasodilation, it is obvious that stimulation of the upper segment of that nerve should cause vasoconstriction. This is the rôle played by the depressor: forming part, as it does, of the cervical sympathetic, it was the nerve which, when cut by Pavy, caused vasodilation in the anterior pituitary and glycosuria, and which, conversely, causes vasoconstriction in this organ when its central or upper end is stimulated. The same effect is produced when the impulses (the nerve being, we have seen, entirely afferent) originate in the heart; the functional activity of the adrenal center being lowered by the contraction of its vessels, that of the adrenals is restrained in proportion and, less adrenal secretion being secreted into the blood, the vessels of the body at large dilate.

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[31] *Cf.* this vol., p. 1021.

[32] Cyon and Aladoff: Bull. de l'Acad. des sci. de St. Petersburg, vol. vii, 1871.

[33] Pavy: Proceedings Royal Soc. of London, vol. x, p. 27, 1860.

Under these conditions, division of the cervical sympathetic, by causing congestion of the anterior pituitary, and, therefore, stimulation of the adrenals, should antagonize (through the rise of vascular tension and blood-pressure caused by the secretion of the latter organs) the depressor action: Hill[34] states, referring to the lowered pressure caused by the vasodilation of depressor origin: "This fall is abolished by section of the cervical sympathetic nerves." Again, as the end-result is due to inhibition of the adrenals and diminution of their secretory activity, other means capable of interfering with their functions should also reduce the vascular tension and the blood-pressure—the results of vasodilation. Oliver and Schäfer have shown, as is well known, that adrenal extracts cause a marked rise of the blood-pressure. Strehl and Weiss,[35] on the other hand, found that clamping of the adrenal veins caused it to decline, and moreover, that on releasing the vessels the pressure would return to the normal.

The depressor nerve does not supply vasoconstrictor fibers to the pituitary body alone, however. Cyon[36] has recently studied the action of this nerve upon the vessels of the thyroid gland and found it very marked. He noticed, moreover, that it influenced correspondingly the abdominal and peripheral vessels. The nerves were found to be distributed to the arteries and were of two kinds, *vasoconstrictor* and *vasodilator*, and to reach them either by way of the superior laryngeals or through the plexus often formed by the depressor with the sympathetic and vagal nerves.

What are the functions of these vasoconstrictor and vasodilator nerves?

As to the *vasoconstrictor* branches, E. Cyon,[37] in a review of his experimental work upon the innervation of the thyroid, states that its "vasoconstrictors are sympathetic fibers." He found, moreover, that the depressor sent a branch to this organ, and that "the heart had a powerful regulator influence" on the quantity of blood circulating through it. On the other hand, a clinician, Murray,[38] observed that "the effect of prolonged administration of thyroid upon the healthy gland is to cause a condition of pallor, some diminution in weight, slight diminution in size of the gland, but without any microscopic evidences of atrophic changes." Here we have precisely the condition produced by a similar process on the pituitary. When constricted the arteries allow less blood—and, therefore, fewer blood-cells—to enter the organ, and its functional activity is reduced. In other words, through the constrictor branches it sends to the pituitary body and to the thyroid, it reduces simultaneously the functions of both organs.

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[34] Hill. *Loc. cit.*, p. 162.
[35] Strehl and Weiss: Pflüger's Archiv, Bd. lxxxvi, S. 107, 1901.
[36] Cyon: Archiv f. d. gesam. Physiol., Bd. lxx, S. 126, 209, 1898.
[37] E. Cyon: Arch. de Physiol., T. x, p. 618, 1898.

The fact that the depressor nerve causes vasoconstriction accounts for the heretofore paradoxical observation that, as stated by Hill, depressor effects cannot be obtained after the injection of strychnine—in toxic doses, I would add. These, by causing general vasoconstriction, affect in a similar way the thyroid and the pituitary body. The depressor producing likewise vasoconstriction, its effects are forestalled. Indeed, Oliver and Schäfer[39] found that depressor effects cannot be obtained "while the arteries are contracted by intravenous injection of suprarenal extract."

These various facts have served to bring out an important practical feature, concerning the avowed purpose of the depressor in the organism: Can we conclude with Cyon that, as he says, this nerve enables the heart "to control the resistance which opposes its evacuation," or, in other words, to provoke vasodilation, when excessive general vasoconstriction causes the blood-column to resist unduly the heart's contractions? If such were the case, why does not stimulation of the central end of this nerve overcome the general vasoconstriction produced by strychnine and adrenal extract? It is evident that this cannot be the main function of the depressor, for, as is well known, the vascular pressure is raised dangerously by various poisons, especially during spasm, and there is no evidence that the depressor fulfills the rôle ascribed to it by Cyon. Its true rôle is of another kind.

This introduces the function of the *vasodilator* fibers which the depressor supplies to the thyroid.

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[38] Murray: Lancet, Mar. 18, 1899.
[39] Oliver and Schäfer: Jour. of Physiol., vol. xviii, p. 230, 1895.

In the light of the conclusions submitted under the preceding heading, the vasodilation observed by Claude Bernard in the maxillary gland indicates increased functional activity, and that this applies to all other organs. As I have shown, moreover, that leucocytes virtually carry on the functions of the thyroid, this vasodilation involves the presence of a larger number of leucocytes in this gland, and therefore, hyperactivity of the organ. As this is manifested by increased secretory activity, an excess of thyroidase should be produced. Now various clinicians, Roger and Garnier,[40] Odoacre Torri,[41] Vincent[42] and others, have observed that in various diseases, including the infections, the thyroid was not only *overactive*, but that it *produced an excess of colloid*, its secretion. In view of the facts (1) that the posterior pituitary incites functional activity in organs belonging to the field of the vagus; (2) that toxic wastes, certain toxins and poisons stimulate the test-organ; and (3) that the depressor nerve also sends fibers to the pituitary body, as shown by Cyon, the manner in which this is brought about suggests itself, viz.: the pathogenic elements of the diseases referred to, which include exanthemata, tuberculosis, typhoid fever, etc., stimulated the adrenal center as usual, and, therefore, the adrenals; but, *in addition* to this, and through the depressor vasodilator fibers to the thyroid, the secretory activity of this organ.

This affords a complete mechanism for automatic defence: The excess of thyroidase to sensitize and soften (as agglutinin) the bacteria and other pathogenic elements, and thus prepare them for destruction; the excess of adrenoxidase to increase the functional activity of the pancreas and leucocytogenic organs, and to charge the blood with trypsin, nucleoproteid granules, and aggressive phagocytes. All these substances, adrenoxidase, trypsin, nucleo-proteid and phagocytes, then unite to destroy the pathogenic agent, previously prepared by the thyroidase to insure its dissolution.

A cardinal feature of the whole defensive mechanism asserts itself in this connection: The vasodilator fibers of the thyroid (some of which also supply the parathyroids) jointly constitute the *thyro-parathyroid secretory nerve*, just as the vasodilator nerves supplied to the adrenals constitute the *adrenal secretory nerve*. Inasmuch as both the thyro-parathyroid and adrenal secretions form part of the blood's bacteriolytic and antitoxic substance, it is evident that both must, in order to insure the full efficiency of the latter, be secreted simultaneously in appropriate proportions. It follows that this function must be governed by a single center, the *adreno-thyroid center*.

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[40] Roger and Garnier: Presse méd., vol. vi, p. 181, 1898.

[41] Odoacre Torri: Policlinico, vol. vii, pp. [illegible], 226, [illegible], 1900.

[42] Vincent: Bull. et mém. de la Soc. méd. de hôpitaux de Paris, 3e. série, [illegible] année, p. [illegible], 1900.

Again, inasmuch as it is through the test-organ that all agents which increase the functional activity of the adrenals and through them the defensive properties of the blood and its cells, enhance oxygenation and function throughout the entire organism, it follows that it must also be through this organ that the functional activity of the thyroid and parathyroids is increased. Whereas, however, the test-organ is a sensitive structure, precisely as the olfactory area of the nasal cavities is a sensitive structure (of which, in fact, it is, as we have seen, the homologue), its impulses are sensory and afferent, and as such, therefore, incapable of inciting or augmenting function directly, it is evident that, as is the case throughout the entire nervous system, they must first of all be converted into motor stimuli. In view of the evidence, histological, clinical, physiological and anatomical, submitted, the posterior or neural lobe of the pituitary not only receives fibers from the test-organ, but it also projects nerve-chains to the base of the brain, which ultimately end in the adrenals and in the thyroid apparatus. It is in the posterior lobe of the pituitary, therefore, that the adreno-thyroid center is located, and when drugs, poisons, catabolic wastes, etc., awaken a protective reaction of the test-organ, it is through this center that the secretory activity of the adrenals and thyroid gland and glandules is activated.

On the whole, all the evidence submitted in the foregoing pages, supplemented by that embodied in the preceding chapters, tends to show: (1) *that the test-organ governs the secretory activity of the adrenals and of the thyroid and parathyroids through the intermediary of a center located in the posterior pituitary body, the adreno-thyroid center;* (2) *that when drugs, poisons, toxins, waste-products, etc., provoke a defensive* *reaction of the test-organ, it is by exciting simultaneously the adrenals and the thyroid apparatus, through the adreno-thyroid center, that it (the test-organ) increases the proportion of adrenoxidase and thyroidase in the blood;* (3) *as adrenoxidase, by hastening metabolism, provokes leucocytosis (including an increase of phagocytes) and an increase of nucleo-proteid and trypsin, and combines with these bodies to form the bacteriolytic and antitoxic constituents of the blood and of its phagocytes, while* (4) *thyroidase sensitizes (as opsonin) the pathogenic germs and substances to render them vulnerable to these defensive constitutents,* it follows: (5) *that the adreno-thyroid center, under the dependence of the test-organ, is the center through which all the body's auto-immunizing functions are governed.*[*]

Hereafter, to avoid confusion, however, I will refer to this center as the "adrenal center" in most instances since the only clearly defined phenomena are those directly ascribable to bodies formed through the agency of the adrenals. It will be understood, thereby, that the "adreno-thyroid" center is meant and that the thyroid apparatus is always stimulated simultaneously.

The participation of the depressor nerve in this mechanism is shown conclusively from another direction:—Cyon[48] observed another important fact, viz., that when he injected iodothyrin—a thyroid extractive—the excitability of the depressor became intense and the vascular pressure declined often to two-thirds of the normal. In one instance, in fact, the animal died suddenly. Cyon ascribes death in such instances to paralysis of the vasoconstrictors. From my viewpoint, it is due to quite another and opposite cause—that previously referred to as of exceeding practical importance: excessive constriction of the vessels of the pituitary and thyroid, and, as a result, arrest of the vital functions owing to deficient supply of adrenoxidase and thyroidase. The general vasodilation produced is but a secondary or epiphenomenon under these conditions. As to the process through which iodothyrin evokes these phenomena, Cyon ascribes it to the fact that it increases the *excitability* of the nerve. This harmonizes perfectly with my own view, since, as I have pointed out, the function of thyroidase is to *sensitize* all cells, to endow them, in other words, with *irritability*. Thyroidase *sensitizes* the nerve directly, therefore, by circulating with adrenoxidase, its ubiquitous companion, in the neurons composing it.

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[*] Investigators refer to the thyroid gland as an organ capable of "governing" certain functions or morbid processes. The above facts show that the thyroid governs nothing; it is only a secreting gland, governed as are all other glands, by a nerve-center—the adreno-thyroid center, from my viewpoint—to which its fluctuations of activity and some of its diseases—exophthalmic goiter, for example—should be ascribed.

[48] Cyon: *Loc. cit.*

In accord with the evidence submitted, the vasoconstrictor effects produced by various drugs, even when administered in toxic doses (as will be shown farther on), are in no case counteracted by the depressor nerve; it is evident, therefore, that (1) *it is not the function of the depressor nerve, as now believed, to cause general vasodilation when excessive general vasoconstriction causes the blood column to offer undue resistance to the heart's contractions;* (2) *in practice the vasodilation witnessed when the central end of this nerve is stimulated experimentally, occurs only when excessive doses of thyroid extract are administered, because it adds to the blood what thyroidase it contains;* (3) *the excitability of the depressor nerve being increased artificially by this excess of thyroidase, it inhibits the functions of the pituitary and thyroid and by thus reducing the proportion of adrenoxidase (and thyroidase) in the blood reduces the vascular tension sufficiently, when toxic doses of thyroid extract are administered, to cause death.*

I must lay stress on the fact that this does not mean that the depressor nerve cannot produce vasodilation: It means only that general vasoconstriction, however marked, cannot itself provoke general vasodilation through the intermediary of this nerve. Inasmuch as it can inhibit the functions of the thyroid gland and anterior pituitary by constricting their arteries, it is able to reduce general oxygenation and metabolism throughout the entire body, including the muscularis of all vessels, thus causing them to relax, *i.e.*, to dilate. As I will show in the twentieth chapter, sleep is produced through the depressor nerve by a corresponding mechanism. Hence the fact that when stimulated experimentally, this nerve produces vasodilation. In other words, *the nerves which have been known as the "depressor nerves" are those through which the adreno-thyroid center regulates the circulation of the anterior pituitary body and of the thyroid apparatus.*

DRUGS WHICH ENHANCE THE DEFENSIVE PROPERTIES OF THE BLOOD BY PROMOTING THE FORMATION OF AUTO-ANTITOXIN.

In his review of the subject of Active Immunity, Lazarus-Barlow,[44] after referring to Pasteur's, Haffkin's and Wright's application of the principle of inoculation in various diseases, writes as follows: "Immunity may be conferred by repeated inoculation with small doses of virulent microörganisms. In this method it is obvious that a direct attempt is made to copy nature. The dose inoculated must, of course, be less than the minimal lethal dose. When the animal has recovered, it is found to possess a certain degree of immunity, and one is able, by gradually raising the dose of virus injected in successive inoculations of the same animal, to raise the degree of immunity which it possesses. Ultimately the animal may withstand with ease a dose equal to many times the dose which would at first have been fatal.

"The most important method we possess for obtaining acquired immunity is that introduced by Salmon and Smith in America. These investigators found that, if the sterilized products of the bacillus of hog-cholera be injected into pigeons, the birds became resistant to subsequent inoculations with the bacillus itself. This method is of vast importance, both from a practical and from a theoretical point of view. . . . . . Numerous examples of immunity acquired in this manner are known, but the most striking are perhaps those obtained in the cases of *B. tetani*, *B. diphtheriæ*, and *B. pyocyaneus*.

"Just as, when conferring immunity by doses of virulent microörganisms, it is necessary to commence with doses far below the lethal dose, and to gradually increase the amount inoculated, so in this method of 'immunization by chemical products' it is necessary to begin with very small doses of the toxin and to gradually increase the dose as immunity is being acquired. If this process be carried out with care, an animal may in time acquire so great a degree of immunity that it will withstand an injection of many hundred times the dose of poison that would have, at first, killed it with certainty. This method is adopted (in some cases in conjunction with inoculation of cultures of living and virulent bacilli) in the preparation of antidiphtheritic serum from horses. There is a limit, apparently, for each animal, beyond which an acquired immunity of this kind cannot be pushed.

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[44] Lazarus-Barlow: "Manual of Gen. and Exp. Pathol.," p. 342, 1904.

"It has been found that an immunity may be acquired after feeding an animal with toxin. Little is known with reference to this method, but it is of great interest in connection with the beneficial results obtained in myxœdema by feeding with thyroids of the sheep."

It is my purpose to show in the following pages that, interpreted in the light of my views, several of our remedies, particularly *some* of those now characterized as "alteratives," behave as do toxins when introduced into the organism, in the sense that they confer upon the patient the power to resist infection. This, from my standpoint, is due, as previously shown, to a compound (adrenoxidase, nucleo-proteid and a zymogen), which, whether as trypsin, steapsin, amylopsin, etc. (according to the zymogen it contains) submits proteids, fats, glycogen, starches, etc., *and bacteria and their toxins as well*, to a process of digestion—a process which, according to the present teachings of physiological chemists, is one of hydrolytic cleavage.

Again, referring to "passive immunity," Lazarus-Barlow writes: "It was found by many observers, among whom Behring stands preëminent, that when an animal has, by any of the methods described above, been immunized against a given infective agent, the blood-serum of that animal, if inoculated into other animals, can confer upon them also an immunity against the same infective agent." The truth of this law he regards as "now firmly established. It has been demonstrated," he adds, "in the cases of rabies, of tetanus, of diphtheria, of pneumonia, and of other diseases. Ehrlich extended the range over which this law holds good by showing that animals may be actively immunized against ricin (the active principle of castor-oil beans) and abrin (the active principle of jequirity seeds), and that the blood-serum of such immune animals is able to confer passive immunity against ricin and abrin respectively in other animals. And Calmette, whose work has been confirmed by Fraser, has shown that the from such a fund of knowledge concerning the effects of individual toxins) each drug shows specific properties especially in the toxic phenomena they produce, which, as I will show, can be accounted for. In *thyroid gland*, for instance, we have an example of a drug capable of raising the blood's asset in auto-antitoxin, since it enhances markedly general metabolism. At a given time, however, the arteries begin to dilate and keep on doing so. The reason for this is plain: thyroidase acting directly, as shown by Cyon, on the depressor nerve, it causes general vasodilation by constricting the arterioles of the pituitary body, reducing thereby general metabolism in the vascular walls. *Mercury* presents another phase. Though likewise able powerfully to raise the activity of metabolism and the blood's supply in auto-antitoxin, it fails to provoke the formation of sufficient thyroiodase to cause the depressor to control the pituitary body—the proportion of thyroidase added to the blood even by toxins being always very small. So marked is the stimulating action on the test-organ and adrenal center, that metabolism is increased to unsafe limits and excessive salivation, tissue destruction occurs, simply because the auto-defensive process has been converted into an auto-destructive process by an excessive quantity of auto-antitoxin in the blood. Not only are bacteria, toxins, etc., destroyed, but the blood-cells, and sometimes the tissue likewise. In *iodine* (and its salts), we have another powerful stimulant of the adrenal system, and the fact that it is the main constituent of the thyro-parathyroid secretion and that it keeps the blood well supplied with opsonins accounts for the value of this drug, since bacteria and the pathogenic elements are prepared for the digestive process to which the auto-antitoxin in the blood and phagocytes submits them. Finally, we have in the *adrenal extractives*, agents which increase directly metabolism in all tissues, and thus provoke the formation of more or less auto-antitoxin. But here we lack the fundamental attribute of the whole process, *i.e.*, they do not stimulate the test-organ directly. Hence their fleeting action, though they are very useful when the blood's most important function, oxygenation, must be promptly and energetically augmented, and when the morbid effects of hypocatabolism must be offset.

Thus, four agents—as instances of others—fully capable of increasing the auto-antitoxic properties of the blood, and, therefore, its auto-antitoxin, show distinct properties in other directions. These points of divergence are all, as I will show, of great importance in practice.

Another important point emphasized by the analysis of the action of the four remedies studied in this chapter is that *it is the small doses which are the beneficial ones,* because they raise the germicidal and antitoxic properties of the blood to a safe limit; while large doses provoke excessive overactivity of the immunizing substances, and its results, destruction of the blood-cells and, in the case of mercury, of the tissues themselves.

To establish the views I advance on a sound basis, a study of the various *antitoxins* is submitted at the close of the chapter. It shows plainly, I believe, that Ehrlich's theory, as far as the side-chain feature itself is concerned, is defective, and that the ductless glands alone afford a sound foundation for the study of all problems concerned with immunity, a fact which I urged in 1903 in the first volume. Ehrlich has never been able clearly to indicate the nature or source of the blood constituents which carry on the immunizing process—a suggestive fact.

As the subjects to be submitted hereafter bear upon questions related to the above: the physiological action of drugs, the pathogenesis of disease, their treatment, etc., all of which are of special interest to the practitioner, they will be presented in a way calculated to facilitate their study: the general principles introduced will be presented in the usual type and the evidence in small type. This plan, however, has entailed the necessity of introducing in the general text (that in large type) a large number of personal conclusions *based upon the evidence herein submitted,* which are necessarily new, since they refer to functions of the organs I have introduced into the problem, or effects produced by them. In each case, therefore, to obviate the introduction of many personal pronouns and, furthermore, indicate that the conclusions reached do not form part of accepted doctrines, they will be distinguished by an asterisk (*) referring to the words "*author's conclusion*" at the foot of the page.

THYROID PREPARATIONS.

Physiological Action.—A dose of thyroid gland may either be stored by the organ itself, or its thyroiodase may be added to the blood at the time, precisely as if the thyroid and the parathyroids had secreted it.* As a result, the functions that thyroiodase subserves, viz., (1) to increase the sensitiveness of all living cells, including those composing the test-organ; and (2) to sustain by direct stimulation the functional activity of the latter as adrenal center, are correspondingly activated.* The immediate effect is an increase of adrenoxidase in the blood, and, therefore, of general metabolism, and increased sensibility of all cellular elements.* The tissue-cells (as well as pathogenic cells, bacteria, parasites, etc.) being thus rendered more vulnerable to the metabolic process, this process is carried on at a rate exceeding greatly that incited by an agent capable only of stimulating the test-organ.* The phase of metabolism most activated, however, is that of catabolism, since the function of thyroiodase is to facilitate the breaking down of cellular elements by rendering them vulnerable to the digestive action of the auto-antitoxin.* Thyroid gland is mainly, therefore, a stimulant of the catabolic process.

The manner in which the thyro-parathyroid secretion (which thyroid gland represents) sensitizes cellular elements and the test-organ, and the mode of action of this secretion on this organ as a direct stimulant, were studied in the preceding chapter, to which the reader is referred. The actual presence of this colloid secretion—thyroiodase—in the lymph and blood has been urged by Hämig,[45] Ehrich,[46] and others. Cerletti and Perusini[47] found it in the arteries and veins. That the addition of a glandular extract containing the active principle or ferment of the colloid should augment the activity of that already in the blood is obvious.

Considerable evidence as to the influence of the thyroid apparatus on metabolism has already been adduced in the preceding chapters. A few additional facts will therefore suffice. In a general review of the subject, Chittenden[48] states that experiments on dogs show that fresh thyroid and iodothyrin have practically the same action in stimulating metabolism of proteid matter and decomposition of fat. This is obviously the result of increased oxygenation, since, as observed by Robert Hutchison[49] and many others, it promotes "the rapidity of combustion."

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* *Author's conclusion.*

[45] Hämig: Archiv f. klin. Chir., Bd. lx, S. 1, 1897.

[46] Ehrich: Bruns's "Beiträge f. klin. Chir.," Bd. xxviii, S. 97, 1900.

[47] Cerletti and Perusini: Jour. of Mental Path., vol. vii, p. 209, 1906.

[48] Chittenden: Trans. Congress Amer. Phys. and Surgs., p. 96, 1897.

[49] Robert Hutchison: Brit. Med. Jour., July 16, 1898.

All the phenomena that this entails are present, moreover. Thus Georgiewsky[50] found that thyroid extract, whether injected or given with the food, caused, in dogs and rabbits, after some time, a rise of temperature, excessive appetite, increase in nitrogen excretion and sometimes glycosuria.

This evidence is controlled by the fact that thyroid gland increases the output of carbon dioxide. Whitney[51] found that there was a marked increase in the amount of CO_2 eliminated by the body, showing increased oxidation of the carbonaceous materials. Conversely, while Albertoni and Tizzoni demonstrated that after thyroidectomy the proportion of CO_2 in the blood was markedly decreased, Magnus-Levy[52] noted that the gaseous exchanges, the temperature and metabolism were all reduced by removal of the thyroid. The increase of excretory products induced by thyroid extract applies as well to catabolic wastes, since large doses produce marked irritation of the organs concerned with their elimination. Thus Ghedini[53] found in 14 animals the liver, kidneys, spleen, and the axillary and inguinal lymph-nodes greatly swollen, infiltrated and inflamed, and concluded that they acted chiefly on organs which eliminated noxious substances. So marked is the increase of catabolism that as shown by Magnus-Levy[54] overalimentation does not prevent emaciation which large doses of thyroid produce.

On the other hand, impairment of the functions of the thyroid apparatus by reducing the efficiency of catabolism, causes imperfectly broken-down—and therefore toxic—wastes to accumulate in the blood. Lange[55] found that removal of portions of the thyroid affected pregnant animals more severely than normal ones. A remnant sufficient for health in the latter did not protect the pregnant animals from spasms or from renal disorders. In pregnant women Lange observed also that, when the customary enlargement and overactivity of the thyroid did not occur, the likelihood that nephritis would appear was greatly increased. Interpreted from my standpoint, this is because the overactive thyroid insures the destruction of the excess of toxic wastes which the fœtus contributes to the blood; if the organ fails to increase its activity, toxic, *i.e.*, imperfectly catabolized, wastes are secreted in abundance by the kidneys, exposing them to nephritis, or if these wastes are retained, puerperal eclampsia occurs. Hypo-thyroidia under these conditions becomes the main cause of puerperal nephritis and eclampsia. Additional evidence to this effect will be submitted in the section on that disease. This indicates the great rôle the thyroid apparatus fulfills in causing destruction of toxic wastes.

That when used in small therapeutic doses, thyroid gland promotes metabolism, but only sufficiently so to enhance nutrition, growth, and the life process itself, is shown by the results obtained with thyroid extract in myxœdema and cretinism. This is fully confirmed experimentally. Thyroidectomy, as is well known, arrests growth and development in animals. Moussu[56] observed that in such animals, thyroid extract soon caused the animals to resume their normal growth and development until a condition was reached when the comparison with the controls was striking. On the other hand, we have in the use of thyroid gland in obesity, evidence to the effect that it can powerfully stimulate catabolism.

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[50] Georgiewsky: Bull. méd., Dec. 1, 1897.
[51] Whitney: Cited by Mosely: Med. News, Sept. 17, 1898.
[52] Magnus-Levy: Zeit. f. klin. Med., Bd. xxxiii, S. 269, 1897.
[53] Ghedini: Centralbl. f. Bakt., Bd. xxxiv, S. 721, 1903.
[54] Magnus-Levy: *Loc. cit.*
[55] Lange: Zeit. f. Geb. u. Gyn., Bd. xl, S. 34, 1899.
[56] Moussu: C. r. de la Soc. de biol., vol. vi, p. 241, 1899.

As thyroid gland promotes catabolism by increasing, through the test-organ and the adrenals, the proportion of adrenoxidase, nucleo-proteid, and trypsin in the blood, it augments its supply of auto-antitoxin.* Being capable also (as opsonin) of sensitizing directly pathogenic germs, thus insuring their destruction by phagocytes and the plasmatic antitoxin, thyroid gland fulfills the two conditions which the body requires to defend itself effectively when infection has occurred.* The blood's antitoxic constituents being, moreover, the bodies which convert the physiological wastes, broken-down cells and all other detritus into benign, eliminable products,* they also prevent the formation of intermediate products, *i.e.*, toxic wastes*—the pathogenic agents in gout and disorders related thereto, including convulsive diseases, eclampsia, tetanus, etc.

Howell,[57] alluding (1905) to the prevailing views as to the functions of the thyroid apparatus and their secretion, writes: "Excision or atrophy of these bodies results in a loss of this secretion and a consequent malnutrition or perverted metabolism in other tissues of the organism. According to the other point of view, less generally held, the function of these bodies is to neutralize or destroy toxic substances formed in the metabolism of the rest of the body." Interpreted from my standpoint, *both* these views are sound, since the identical process which sustains nutrition and metabolism, is that which insures neutralization of toxic substances. We have seen that the rôle of the thyroid in metabolism is supported by a multitude of facts; this applies as well to its function in the destruction of poisons, the latter function being—as I view it—but an exacerbation of the former.

Recent clinical observations have extended the defensive functions of the thyroid to general infections. Thus, Roger and Garnier[58] examined the thyroid glands of 33 cases after death from various infections, scarlet fever, measles, diphtheria, smallpox, typhoid fever, cerebro-spinal meningitis and septic meningitis. Congestion and hypertrophy were found in all. The clinical histories did not include pain in the thyroid. They suggested that these local disorders might be due to overactivity of the gland having for its purpose the destruction of the specific poisons. Odoacre Torri[59] also found that during infectious diseases the gland was overactive and that it secreted an inordinate amount of colloid secretion. He noted, moreover, a marked epithelial proliferation, which, from my standpoint, means an abundance of iodine-laden leucocytes. In common with other investigators, however, he erroneously regards the colloid itself as the bactericidal product and the excessive secretion as a defensive process.

Vincent[60] observed enlargement of the thyroid in rheumatism and regards it as "an expression of increased function to antagonize infection." He found the organ sensitive and enlarged in 11 out of 17 cases of typhoid fever, in which these signs appear early. The results obtained by Leopold-Lévi and de Rothschild[61] in 100 cases to which they administered thyroid extract also led them to conclude that the thyroid "acted as a regulator of nutritional ferments as well as of the defensive ferments" of pancreatic origin, in accord with the view I had advanced over two years earlier. They point, moreover, to the fact that thyroid insufficiency predisposes to infection and auto-infection. Morin[62] also emphasized recently the defensive rôle of the thyroid as shown by the liability to tuberculosis and other infections of individuals suffering from congenital myxœdema. In 348 ordinary cases of tuberculosis, 192 showed marked atrophy of the thyroid. He regards this phenomenon as the main cause of the prominence of the thyroid cartilage in these cases. Such cases fared badly, as a rule, while those in which the gland was normal or enlarged yielded promptly to remedies. Bonnet[63] has already observed that in cases of athrepsia, the addition of small doses of thyroid extract to the usual remedies and diet measures, promptly turned the tide in favor of the patient, while Reid Hunt,[64] found that thyroid feeding rendered "white mice much less susceptible to the toxic action of acetonitril."

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* *Author's conclusion.*

[57] Howell: "T. B. of Physiol.," p. 774, 1905.

[58] Roger and Garnier: Presse méd., vol. vi, p. 181, 1899.

[59] Odoacre Torri: Policlinico, vol. vii, pp. 148, 226, 280, 1900.

[60] Vincent: Bull. et mém. de la Soc. méd. des hôpitaux de Paris, 3 série, 23 année, p. 596, 1906.

The marked increase of colloid which Roger and Garnier and Torri observed under the influence of infectious diseases corresponds with that of Wright's opsonin formed under the influence of inoculations with tuberculin and kindred bodies. Opsonin and thyroidase, as I have pointed out, being one and the same substance, thyroidase, when we administer thyroid gland, we contribute opsonin directly to the blood. As thyroid gland also promotes active metabolism by stimulating the test-organ, we have precisely the effects produced by inoculations, since it is through a similar process that they cause the appearance in the blood of what Wright has termed "bacteriotropic" substances. Hence the fact that, as I have myself observed, thyroid extract is an effective agent in the treatment of tuberculosis and other infections.

Untoward Effects.—Small doses administered at too short intervals, or large therapeutic doses cause the blood-pressure to fall, although the proportion of auto-antitoxin in the blood may not be sufficient to cause hæmolysis, and thus normally to awaken the protective intervention of the depressor nerve.* This is due to the fact that the thyroiodase which the thyroid preparation introduces into the blood, by accumulating therein, gradually raises directly the excitability of this nerve.* Though stimulated artificially, the nerve fulfills its normal rôle, and by causing vasoconstriction of the arteries of the pituitary and thyroid, inhibits their functions.* Less thyroiodase and adrenoxidase (which jointly aid in sustaining the vascular tone) being secreted, the arteries relax passively.*

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* *Author's conclusion.*

[61] L. Lévi and de Rothschild: C.-r. de la Soc. de Biol., vol. lx, p. 971, 1906.

[62] Morin: La Presse méd., vol. xiv, p. 622, 1906.

[63] L. Bonnet: Semaine méd., vol. xxiii, p. 212, 1903.

[64] Reid Hunt: Jour. of Biolog. Chemistry, vol. i, p. 33, 1905-06.

Oliver and Schäfer, Haskovec, Gley, Langlois, and several other investigators have all found that experimental—and therefore large—doses of thyroid extract caused vasodilation and lowered the blood-pressure. Human thyroid extract produces a similar effect as observed by Guinard and Martin,[65] who used the thyroid taken from an executed criminal, immediately after death. The influence on the vessels is very prompt: Béla von Fenyvessy[66] found that it lowered the blood-pressure in rabbits, beginning a few seconds after the injection. Patta[67] found that thyroidin lowered the blood-pressure in a manner directly opposed to suprarenin.

If the use of large doses is persisted in, the excessive vasodilation produced by the remedy becomes such that, in accord with Marey's law,* the rapidity of the heart-beats, *i.e.*, the pulse, is greatly increased. The blood being caused to accumulate in the great central trunks, the splanchnic area, the quantity circulating through the lungs is reduced* and, the absorption of oxygen being inadequate,* dyspnœa ensues, and sometimes cyanosis. General oxygenation, owing to this cause and to the diminution of adrenoxidase,* being lowered, the heart's action becomes irregular. The skeletal muscles being affected in the same way,* general weakness, trembling and muscular pains (owing to the accumulation of toxic wastes) may be complained of. Vertigo, mental depression may likewise occur.

When the cutaneous arterioles are also dilated, they admit an unusual volume of blood into the capillaries;* causing superficial congestion, hyperthermia, pruritus and tingling. A similar condition of the gastric capillaries causes nausea and vomiting; of the intestines, diarrhœa; of the brain, insomnia; of the meninges, headache. These symptoms are usually transitory if the use of the remedy is discontinued, but if it is persisted in, it may produce syncope. The morbid symptoms sometimes persist after withdrawal of the drug. Exertion, when large doses of thyroid gland are being used, is dangerous, owing to the deficient nutrition and weakness of the cardiac muscle.

Various other symptoms have been recorded: transitory aphasia with monoplegia and unilateral anæsthesia (Béclère); epileptoid convulsions (Henry); a condition resembling uræmia (Schmidt), etc. Two fatal results were reported by Murray; two by Vermehrer; one by Foulis; one by Stabel—but all in cases of myxœdema in which the doses were large. Many others have been reported. Popoff,[illegible] who refers to these cases, states, however, that thyroid preparations produce "deplorable effects capable of causing death not only in myxœdematous subjects, but also in cases of obesity, psoriasis and even in healthy subjects." Georgiewsky,[illegible] even in animals killed by the drug, found, in accord with Murray's observation, that the thyroid gland was "pale, yellowish and diminished in size," although there was pronounced atrophy of the adipose tissue and of the muscles and intense congestion of other organs, the kidneys, bulb, brain, etc. This points to the sequence of events: (1) violent hypercatabolism of the body constituents which are always the first to yield, the fats; (2) reaction of the depressor; (3) death through the presence of enough thyroidase in the blood to excite violently the depressor and cause it to paralyze the pituitary body and thyroid gland by unduly constricting their vessels.

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* *Author's conclusion.*

[65] Guinard and Martin: C. r. de la Soc. de biol., 10 série, vol. vi, p. 161, 1899.

[66] Béla von Fenyvessy: Wien. klin. Woch., Bd. xiii, S. 125, 1900.

[67] Patta: Inaug.-Dissert., Pavia, 1904.

Therapeutics.—As this feature of the subject has been treated at length in the first volume (pages 708 to 737 inclusive) only a brief reference will be introduced here.

The use of thyroid is deemed dangerous by some. In truth, there are but few remedies whose effects can be controlled with more accuracy, if the symptoms it provokes are watched, and if fresh preparations of thyroid are used. Small doses, ½ to 1½ grains (0.03 to 0.1 gram) of the desiccated gland, seldom prove excessive. The pulse may be raised slightly, and there may be a rise of temperature of ½ to 1° F. (0.3 to 0.6° C.), but this is not due to abnormal action; it is the result of enhanced metabolism—an expression of the remedy's beneficial or "tonic" action. Conversely, when larger doses are given, such as those employed in the treatment of obesity (beginning with 2 grains [0.13 gram] three times daily and gradually increased), the hypercatabolism to which the reduction of flesh is due keeps the patient on the verge of depressor action, and, more or less suddenly, the pulse becomes faster. Instead of being firm or somewhat harder than usual, as is the case when the "tonic" phase of thyroid action prevails, the pulse is softer and yields readily to pressure. The patient may complain of vertigo, weakness and palpitations, etc., altogether a symptom-complex indicating functional torpor—though the face may be flushed by dilatation of the arterioles. The two conditions are radically different, therefore, and the danger signals of depressor action are clearly defined.* It is always best to discontinue the drug when the latter occur, and resume only with smaller doses.

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* *Author's conclusion.*

[illegible] Popoff: Arch. gén. de méd., Oct., 1899.

[illegible] Georgiewsky: *Loc. cit.*

Murray[70] also states that "the earliest and most common symptom is the increased frequency of the pulse. Other symptoms are violent palpitation, fine tremor of the hands, flushing and moisture of the skin, and, in case of large doses, emaciation." Easterbrook,[71] after using thyroid gland in about 100 cases in sufficient doses to produce thyroidism, concluded that "indubitably" it was "a profound catabolic stimulant."

The principles formulated in the foregoing pages account for the beneficial effects thyroid preparations have afforded in various disorders:—

Their mode of action in *myxœdema* and *cretinism* is self-evident, since by enhancing the irritability of all cells and stimulating the adrenal functions, thyroid preparations supply the organism with precisely the two sources of energy that incite and sustain the vital process. In the various diseases due to lowered catabolism or the accumulation of toxic wastes in the blood, such as *tetany, puerperal eclampsia, epilepsy,* the disorders of *menopause, asthma* and *rheumatoid arthritis,* their beneficial effects are but the counterpart of their action after thyroidectomy: by promoting catabolism, they insure the conversion of the pathogenic elements into readily eliminable end-products. Exaggeration of this process accounts for the emaciation caused in *obesity* and its benefit in Dercum's disease, *adiposis dolorosa.* The nutrition of osseous tissues and the processes of repair being enhanced, the improvement observed in *osteomalacia, rickets, osteomyelitis* and delayed union in *fractures* is also easily accounted for. Their action on the adrenal center leading to the accumulation of adrenoxidase in the blood, explains their efficacy in *hæmorrhages* of various kinds and hæmophilia, since adrenoxidase is the fibrin ferment,* the underlying factor in the formation of the blood clot.

In infections, including *asthenic pneumonia,** the *exanthemata* of childhood, *tuberculosis* and *typhoid fever,* the value of thyroid preparations—in small doses—is readily explained. They attack directly the pathogenic organism by rendering it vulnerable to the attacks of phagocytes and the blood's auto-antitoxin—and insure the work of destruction by stimulating the test-organ, the governing center of the body's defensive mechanism.* (See also Thyroid Organotherapy, vol. i, p. 708.)

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* *Author's conclusion.*

[70] Murray: Lancet, March 18, 1899.

[71] Easterbrook: Lancet, Aug. 6, 1898.

MERCURY.

Physiological Action.—Whether administered by the mouth, injected subcutaneously, or rubbed into the skin (dissolved therein by the constituents of the sebaceous secretion), mercury and its salts are taken up by leucocytes and carried to all tissues.

Although toxic effects occur after the ingestion or inhalation of metallic mercury, this metal cannot, as shown by Hermann,[72] penetrate normal epithelium in any part of the body. The metal is found condensed upon the epithelium. This was confirmed by Hoffmann, Rohrig, Bärensprung, Neumann and Fleischer, and others.[73] The reason for this becomes plain in view of the fact that it is taken up by leucocytes. Conti and Zuccola[74] found that mercury, whether administered by the mouth or hypodermically, was always carried to the tissues by these cells. We have seen in the preceding chapter that Stassano, Besredka and Montel had also observed that they ingested mercurial salts, including calomel, introduced into the blood by injections or inunctions. Montel[75] ascertained, moreover, that this rôle was carried on by the neutrophiles and the large mononuclears. This was confirmed by Collet,[76] who found also that lymphocytes and the red corpuscles took no part in the process. Stassano[77] isolated the red corpuscles from the leucocytes and found mercury in the leucocytes only. Carles[78] reached a similar conclusion. Almkwist[79] holds that in the intestine mercury forms a sulphide with sulphuretted hydrogen, and observed leucocytes containing fine yellow granules of the sulphide between the epithelial cells of the intestine. He also found this sulphide in the blood, lymph and tissue fluids. As other observers, including Rindfleisch and Fürbringer[80] and Chittenden[81] have found mercury in solution in the body juices in the form of albuminates, the metal, in the light of the foregoing facts, must be derived from the tissues into which they have been secreted by their normal carriers, the leucocytes. Barthe and Mongour[82] conclude that the mercury must first destroy these cells to be liberated, but the evidence I have submitted sufficiently demonstrates that such destruction is unnecessary.

That mercury does not act directly upon the tissues is shown by the fact that it may accumulate in the organism, and remain practically inert therein. Referring to the labors of Vajda and Paschkis,[83] Schuster,[84] Balzer and Klumpke,[85] and others, Wood[86] states that "the evidence in favor of the storing up of mercury in the system is overwhelming."

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[72] Hermann: "Lehrbuch d. exper. Toxikologie," Berlin, 1874.

[73] Hoffmann, Rohrig, Bärensprung, Neumann and Fleischer: Cited by A. A. Chittenden: Bull. Johns Hopkins Hosp., May, 1899.

[74] Conti and Zuccola: Riforma médica, Mar. 17, 1906.

[75] Montel: Gaz. hebd. de méd. et de chir., Apr. 21, 1901.

[76] Collet: Lyon médical, June 14, 1903.

[77] Stassano: C. r. de l'Acad. des sci., 1898.

[78] Carles: *Loc. cit.*, p. 32.

[79] Almkwist: Nord. med. Ark., Afd. 2, No. 6, 1903.

[80] Fürbringer: Virchow's Archiv, Bd. lxxxii, S. 491, 1880.

[81] Chittenden: Bull. Johns Hopkins Hosp., May, 1899.

[82] Barthe and Mongour: Jour. de méd. de Bordeaux; Med. Age, Dec. 26, 1906.

[83] Vajda and Paschkis: "Ueber d. Einfl. d. Quecksilber," Wien, 1880.

[84] Schuster: Zeitsch. f. klin. Med., Bd. vii, S. 80, 1884.

[85] Balzer and Klumpke: Rev. de méd., vol. viii, p. 308, 1888.

[86] Wood: *Loc. cit.*, thirteenth edition, p. 484, 1906.

The various salts of mercury owe their therapeutic value to the energy with which they stimulate the test-organ.* In minute doses they promote nutrition, *i.e.*, act as a tonic, because, by stimulating the test-organ, they increase the secretory activity of the adrenals, and enhance, therefore, general oxygenation and metabolism.* The function of the pancreas, the thyro-parathyroid apparatus and the leucocytogenic organs being correspondingly activated, the quantity of auto-antitoxin in the blood is augmented.*

Its powerful stimulating action on the adrenal center is shown in various ways. Like all lesions of the anterior pituitary attended with local hyperæmia, mercury provokes glycosuria.

Salkowsky[57] found that "mercury diabetes lasts longer than the other artificially-produced diabetes, persisting sometimes eighteen days" after the causative doses. It was also noted by Reynoso, Rosenbach, Bouchard and Cartier.[58] It is commonly observed in rabbits, when too large doses (which paralyze the adrenals) are avoided. As emphasized by Cartier, it is not by causing grave hepatic lesions that mercury evokes diabetes; as I have shown,[59] a marked excess of adrenoxidase in the blood is the cardinal factor in its production, since this greatly enhances the functional activity of the pancreas, and, therefore, the production of amylopsin, the ferment which converts glycogen into sugar. That the adrenals are hyperactive was ascertained by Moulinier,[60] who found the adrenals intensely congested in slow mercurial poisoning, and invariably hypertrophied. He observed, moreover, that in subjects who suffered from slow mercurial intoxication, even minute doses of adrenalin hastened death; and moreover, as a corollary to this fact, that individuals to whom mercury and adrenalin were given simultaneously died sooner than when adrenalin was given alone. He concluded, therefore, that the action of mercury is added to that of adrenalin. The reason for this is obvious: the mercury doing harm by overexciting the adrenals, adrenalin added fuel to the fire, the excess of adrenoxidase—the albuminous hæmoglobin—being of course the harmful agent. Under these conditions mercury should prove useful in conditions attended with deficient hæmoglobin. Semmola[61] noted that in syphilitics, the hæmoglobin rose markedly under mercury, within seven or eight days. As shown by Cervello[62] the same effect is produced in animals.

The stimulating action of mercury on the pancreas is illustrated further on. That on lymphatic organs is sufficiently marked to have led Jullien[63] to ascribe to it the striking effects of this drug in syphilis. That leucocytogenesis is actively stimulated was conclusively shown by the experiments of Koslowsky.[64] Not only was the proportion of older cells reduced, but that of young cells was increased. Kupferwasser[65] found that the number of young leucocytes in the blood was considerably increased in normal subjects, and in syphilitics when the treatment was not too prolonged. A contrary effect is produced, however, when the drug is taken in toxic doses, *i.e.*, in sufficient quantities to depress the test-organ.

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* *Author's conclusion.*

[57] Salkowsky: Virchow's Archiv, Bd. xxxvii, S. 346, 1866.

[58] Cartier: Thèse de Paris, 1891.

[59] *Cf.* this vol., p. 1021.

[60] Moulinier: Archives de méd. navale, vol. lxxxiv, p. 265, 1905

[61] Semmola: Presse méd., Sept. 15, 1889.

[62] Cervello: Jour. des practiciens, Jan. 12, 1901.

[63] Jullien: "Maladies Vénériennes," 1886.

[64] Koslowsky: Thèse de St. Petersburg.

[65] Kupferwasser: Arch. des sci. biol. de St. Pétersburg, vol. vi, 1898.

The experimental investigations upon the influence of mercury on metabolism that have been recorded are worthless in that the ruling element of the problem, the relative influence of dosage, was not taken into account, the animals thus receiving toxic doses which paralyzed the adrenal center in practically every instance. The clinical evidence on the subject is alone instructive, therefore. Levi,[96] in a study of 252 patients suffering from syphilis, "found that the mercurials increase organic combustion and hasten metabolism in this condition," a proof that the blood's asset in auto-antitoxin is increased. That nutrition is enhanced is shown, moreover, by the increase of weight observed by Liégeois,[97] Armaingaud and Martin-Damourette,[98] while Keyes,[99] Wilbouchewitch, Gaillard, Hayem, Robin, and others noted besides this, a marked increase of red corpuscles. Similar results were obtained by Schlesinger[100] in dogs and rabbits.

This accounts for the fact that various preparations of mercury, calomel particularly, have always occupied a high place among the agents known to abort disease. Daly, of Pittsburgh, found calomel of great value in diphtheria, recommending its use until the stools became green. Illingworth[101] found the biniodide or calomel extremely effective for the jugulation of various infectious diseases such as scarlet fever, diphtheria, measles, chickenpox, pertussis, typhoid fever, pyæmia, puerperal fever, etc., and his observations in some of these diseases have been confirmed by Dukes, Neale, Lloyd Brown, and others.

The immunizing process is most active in the liver, an action which becomes manifest when sufficiently large doses of mercury to produce purgation are given. Mercurial purgatives do not, as generally believed, produce their effects by increasing the secretion of bile—which is a mere epiphenomenon when it occurs—but by increasing the germ- and poison-destroying properties of the hepatic blood.* The green stools produced are rich in biliverdin, *i.e.*, adrenoxidase.*

It is believed by many that mercury produces its beneficial effects by increasing the biliary secretion, but the investigations of Pfaff and Balch, and Joslin,[102] have shown that the bichloride and calomel not only do not increase the flow of bile in patients with biliary fistula, but that they tend rather to decrease it. This indicates that the benefit derived from mercury is due to the greater antitoxic activity of the hepatic blood and not to an increase of fluid. Again, when calomel is administered to healthy individuals in suitable doses, green liquid stools, as is well known, are produced. The belief that this was due to an increase of bile was eventually replaced by the view that the color was the result, as suggested by Traube and Stillé, of the presence of a mercurial compound. But the analyses of Simon,[103] Golding Bird,[104] and Michéa[105] failed to show that the metal was present in any form. The investigations of Simon and Michéa revealed an important fact, however, viz.: the presence in the stools of bile *pigments*, and particularly *biliverdin*, in large quantity. As I have shown in various parts of this work,[106] however, bilirubin is oxidizing substance, *i.e.*, adrenoxidase; the large quantity of bilirubin in the stools is evidently due, therefore, to excessive activity of the adrenals.

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* *Author's conclusion.*

[96] Levi: Cited by Jour. Amer. Med. Assoc., May 12, 1906.

[97] Liégeois: Gaz. des hôpitaux, vol. xlii, pp. 347, [illegible], 363, 371, [illegible], [illegible].

[98] Armaingaud and Martin-Damourette: Manquat: *Loc. cit.*

[99] Keyes: Amer. Jour. Med. Sci., Jan., 1876.

[100] Schlesinger: Arch. f. exp. Path., Bd. xiii, S. 317, 1881.

[101] Illingworth: "Abortive Treatment of Febrile Disorders," [illegible].

[102] Joslin: Cited by Hare, "Practical Therapeutics," p. [illegible], 1904.

[103] Simon: Animal Chemistry, Sydenham Soc. Trans., ii, p. [illegible].

[104] Golding Bird: London Med. Gaz., vol. i, p. [illegible], [illegible].

The antitoxic process carried on in the liver under the influence of a mercurial purgative is supplemented by a similar process in the intestine.* The excess of adrenoxidase in the blood raises the secretory activity not only of the pancreas, but also of all the intestinal glands.* A large volume of intestinal juice rich in pancreatic juice, nucleo-proteid and adrenoxidase, *i.e.*, in auto-antitoxin similar to that in the blood, is thus produced, which flushes the intestinal canal and sterilizes it.*

The manner in which the various components of the intestinal juice are produced and their physiological function have been reviewed in the fourteenth chapter, to which the reader is referred. The stimulating influence of mercury on the pancreas is generally recognized. Potter,[107] for instance, states that in full doses, continued, the preparations of mercury "overstimulate the glands, especially the pancreas." In a case reported by Copland,[108] in which death occurred during excessive salivation, the pancreas weighed, *post-mortem*, four ounces, was red and congested, while its ducts were dilated. Arnozan and Vaillard[109] observed marked evidences of overactivity in the pancreas of rabbits treated about one month with corrosive sublimate.

The powerful stimulating action of mercury on the test-organ, *i.e.*, on the adrenal center,* renders it a powerful cardiac stimulant. The adrenal secretion not only sustains the functional activity of the right heart, but the improved oxygenation of the entire body increases the nutrition of the organ.* Again, by stimulating catabolism, it also relieves the blood of any excess of wastes,* and thus antagonizes undue arterial tension and vascular resistance.

Murray[110] regards blue pill, 5 grains (0.3 gm.) every night, as "the basis of treatment in all cases of weak, dilated, irritable and irregular heart where there is resistance in the arterial system." Sir William Broadbent, Allbutt, Dickinson, Morison[111] and others have all recommended small doses of mercury to reduce "impedimental conditions of vascular tension." William Pepper has also emphasised the value of mercury in heart failure.

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* *Author's conclusion.*

[105] Michéa: L'Union méd., vol. ii, p. 495, 1848.

[106] *Cf.* vol. i, pp. 115, 119, 128, in the first two editions.

[107] Potter: "Materia Medica, Pharm. and Therap.," eighth edition, 1901.

[108] Copland: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 487, 1906.

[109] Arnozan and Vaillard: Jour. de méd. de Bordeaux, 1893.

[110] Murray: Phila. Med. Jour., June 23, 1900.

[111] Morison: Lancet, Oct. 28, 1899.

Mercury is an energetic diuretic. This is due (1) to the fact that it increases considerably the intrinsic metabolism of the kidneys, and, therefore, their functional activity—as it does that of all other organs—and (2) to the passage through the kidneys of an unusual proportion of excretory products, including a portion of the drug itself. Its prolonged use exposes the kidneys to grave disorders.

Rosenheim[112] found, in experiments upon dogs, that when mercury acted as a diuretic, it did so by stimulating the renal epithelium, and by flushing the renal vessels. Bieganski[113] and Stintzing[114] and others also attributed the local lesions directly to the metal. Fürbringer,[115] in a study of the statistics of the subject, found that 8 out of 100 syphilitic subjects suffered from nephritis when under mercurial treatment, but that withdrawal of the drug was usually followed by recovery. Swan[116] reported a case which had reached the stage of parenchymatous nephritis in which the urine, examined at short intervals, was found to contain mercury one year and twenty-nine days after the last dose had been administered. In a case of sublimate poisoning observed by Chauffard[117] there was complete anuria during five days. H. C. Wood, Jr.,[118] observed hæmorrhagic nephritis in several cases of corrosive sublimate poisoning.

Untoward Effects.—The therapeutic dose of mercury *i.e.*, the quantity that will stimulate sufficiently the test-organ to protect the body against infection, is very small.* Beyond this limit excessive oxygenation of the blood occurs and digestive activity of the auto-antitoxin becomes such that it provokes more or less serious disorders.* This is due to the fact that while the adreno-thyroid center is stimulated very actively (through the test-organ) by mercury, the proportion of thyroidase produced is only sufficient to excite the depressor nerve (thus inhibiting the formation of auto-antitoxin) when the metal is taken in very large or toxic doses.*

The earliest indication that mercury is being given in excess is *salivation*, due to undue stimulation of the salivary glands. The intrinsic metabolism becomes such* that enormous quantities of saliva are sometimes voided. The glands often become enlarged and tender. Evidences of increased general metabolism,* slight fever and restlessness may also appear at this time, accompanied by increase of tendon reflexes, and, in rare cases, by hallucinations.

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* *Author's conclusion.*

[112] Rosenheim: Zeit. f. klin. Med., Bd. xiv, S. 170, 1888.

[113] Bieganski: Arch. f. klin. Med., Bd. xliii, S. 177, 1888.

[114] Stintzing: Münch. med. Woch., Bd. xxxv, S. 1, 1888.

[115] Fürbringer: Med. Week, vol. ii, p. 234, 1894.

[116] Swan: Amer. Jour. Med. Sci., Jan., 1904.

[117] Chauffard: Semaine méd., vol. xxv, p. 13, 1905.

[118] H. C. Wood, Jr.: Amer. Med., Dec. 27, 1902.

While the stimulation of the test-organ, which indirectly increases the auto-antitoxin in the blood, is brought about by the mercurial carried directly to that organ by leucocytes, the bulk of the drug which is secreted in the tissues by these cells, is converted, as is well known, into an inert albuminate. Chittenden,[119] for instance, writes as the result of a careful study of the question: "Just how the solution of mercury by the body juices is effected, and what part is played by the albuminous constituents, we cannot say, but that solution is effected and the mercury eliminated as an albuminate seems to be true." As it is this compound which circulates in the pituitary body, the test-organ is not caused to react.

The proteolytic activity, to which the intestinal juice owes its bacteriolytic and antiseptic properties, may be sufficient in cases of poisoning to cause lesions in intestinal mucosa, by a process similar to that of hæmolysis in the blood proper. These lesions are now attributed to a direct action of the mercury, but such is evidently not the case when even large therapeutic doses are taken, for they may be produced when mercury is applied externally. In Sackur's fatal case,[120] for example, a single inunction sufficed to provoke them. In Audry's case[121] hypodermic injections of the metal caused numerous ulcers in the intestine, etc. Interesting in this connection is a case reported by Alfred Berliner[122] in a syphilitic woman, six months pregnant, in whom inunctions caused violent enteritis. On withdrawing the drug the latter disappeared, but recurred at once on resuming its use. After delivery, however, the inunctions produced no ill effects. The use of mercury has often been pointed out as dangerous in pregnant and puerperal women. The reason for this is self-evident, in view of the fact that during pregnancy, "the *anterior lobe* of the pituitary body" as shown by Comte, Launois and Mulon,[123] is "in a manifest condition of hyperactivity." As mercury violently stimulates precisely the anterior pituitary (the test-organ), and the symptoms of mercurial poisoning are those of excessive activity of the adrenals, it is only normal that mercury, during pregnancy or parturition (the anterior pituitary remaining active until all toxic wastes in the body are destroyed), should cause poisoning.

As to salivation, the rôle of adrenoxidase in the process of excessive auto-antitoxin formation is well illustrated by the fact that adrenal extract in toxic doses was found by Gourfein[124] to cause salivation, among other symptoms, in animals. Taramasio[125] also observed frothing. As mercury acts by stimulating the adrenal mechanism, the cause of this symptom is obvious. Cushny,[126] who refers to the fact that many liters of saliva are sometimes poured out in twenty-four hours, states that "the salivation and stomatitis which are so frequently seen under mercurial medication are obviously not due to the local action of the drug on its way to the stomach, for they occur equally readily when it is applied by hypodermic injection or by inunction." Nor are salivation and stomatitis due to a local effect of the remedy while being ingested, since they occur as readily when mercury is used by hypodermic injection or by inunction. Indeed, Bockhart,[127] de Renzi,[illegible] Galippe[illegible] and others found that the local application of mercurial preparations cured stomatitis due to ingested mercury. Nemser[illegible] ascertained experimentally, through gastric fistulæ, that the gastric juices had little or no effect on calomel, even when the salt was left in the stomach over an hour.

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[119] Chittenden: *Loc. cit.*
[120] Sackur: Berl. klin. Woch., Bd. xxix, S. 618, 1891.
[121] Audry: Lyon méd., Apr. 15, 1888.
[122] Alfred Berliner: Allg. med. Centr. Zeit., vol. lxxiii, p. 612, 1904.
[123] Comte, Launois and Mulon: Ann. de gynéc. et d'obstét., Jan., 1904.
[124] Gourfein: Rev. de la Suisse rom., vol. xv, p. 513, 1896.
[125] Taramasio: *Ibid.*, vol. xxii, p. 599, 1902.
[126] Cushny: *Loc. cit.*, p. 643.
[127] Bockhart: Monats. f. prakt. Derm., Aug., 1885.

MERCURIALISM.—When the therapeutic use of mercury is injudiciously prolonged and in subjects who are exposed by their occupations to the continuous absorption of this metal, another order of phenomena is introduced, *i.e.*, those due to chronic poisoning—another manifestation of uncontrolled metabolism.*

The earliest symptoms of this condition include a metallic taste, soreness and swelling of the gums, a bluish-red or gray color along the peridental sulci and the fœtid breath which mark the onset of *active* mercurialism. Unless the use of the drug ceases, the destructive process extends downward and around the teeth, causing these to fall out; gangrene of the gums and jaws, and hæmorrhages may then ensue. The tongue, the entire mucosa of the mouth, especially where it overlies considerable soft tissue, *i.e.*, the cheeks and lips, undergo a similar destructive process. If the use of the drug be persisted in, death may follow from exhaustion and inanition. If its use be stopped when the ulcerative process has penetrated the cheeks, the patient remains scarred and disfigured.

Gastro-intestinal disorders, anorexia, nausea, vomiting, gastric pain, colic, diarrhœa alternating with constipation, and intestinal ulceration similar to that observed in the mouth are also observed. Marked anæmia and pallor, emaciation and great muscular weakness occur, even though gastro-intestinal disorders be mild, and death may ensue.

All these phenomena are due to excessive oxygenation and to the proteolytic activity of the blood's auto-antitoxin.* They are especially marked where the epithelium of the gums is destroyed by the contact of "tartar," carious teeth, etc., and the underlying elements are exposed to the air.* The adrenoxidase being greatly in excess in all tissues, the air furnishes an endless quantity of oxygen to its catalytic agent, *i.e.*, the adrenal principle, and the gums and other tissues are destroyed through a local digestive process.*

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* Author's conclusion.

[illegible] de Renzi: Revista clinica e therap.; Physician and Surgeon, Apr., [illegible].

[illegible] Galippe: Jour. des Conn. Médic., pp. [illegible], [illegible], [illegible], [illegible].

[illegible] Nemser: Zeit. f. physiol. Chemie, Sept. 6, [illegible].

The destructive process is very active in the blood, owing to the presence of adrenoxidase in the plasma, and of the red corpuscles, which deal out adrenoxidase as fast as needed to sustain the morbid process.* Both the red corpuscles and the leucocytes are actively digested, and the general nutrition is correspondingly impaired. The broken-down cells, etc., being no longer converted into eliminable products, they form the fatty, fœtid substance found in the vessels after death.

That the proteolytic, *i.e.*, digestive activity of the blood, is greatly increased by mercury has been sufficiently emphasized by the evidence already submitted. The morbid effects are evidently not due to a local action of the drug, since it is most likely to occur when it is given by inunction. The rôle of adrenoxidase in the morbid process is also shown by the pernicious influence of concomitantly-given adrenalin, emphasized by Moulinier.[151]

The oxidizing action of the blood-fluids on mercury has been repeatedly noticed by investigators. It has, in fact, been considered a necessary factor of its combination with the albumins of the tissues, into which, we have seen, it is secreted by the leucocytes after being submitted to the action of the ferments—including adrenoxidase—in these cells. Thus, Hermann[152] states that "we must suppose some supplementary oxidation as a result of the tissue juices."[153] Cushny[154] also states that "even the metal may be oxidized and absorbed when it is applied to the living surfaces or injected into the blood in a state of fine division."

That the destructive action cannot be a local one is shown by the smallness of the dose that is capable of producing it, along with general phenomena. Thus Lewin[155] reported the case of a man who, after a subcutaneous injection of $^1/_4$ grain (0.016 gm.) of salicylate of mercury, had stomatitis, with ulceration, together with acute nephritis (anuria and albuminuria). The temperature rose to 40° C. (104° F.) and death was barely averted. The biniodide employed in intra-uterine injections, 1 to 3000 solution, caused acute mercurial poisoning in a case of Young's.[156] Inunctions of the gray ointment are particularly dangerous in this connection. Out of 630 cases in which mercurial ointment was used by the medical officer of a workhouse in Belgium[157] to rid the inmates of vermin, 50 were made very ill, one case proving fatal, although the quantity used was but a trifle more than a drachm (4 gms.). Kraus[158] observed a case in which, after the second hypodermic injection of 0.1 gm. ($1^1/_2$ grains) of calomel, intense intestinal symptoms accompanied by perforation and anuria, occurred. Repeated 1-grain (0.065 gm.) doses of calomel used hypodermically, caused death in a case observed by Runeberg.[139] The old and feeble are especially vulnerable to the toxic action of mercury.

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* *Author's conclusion.*

[151] Moulinier: *Loc. cit.*

[152] Hermann: *Loc. cit.*

[153] Manquat: *Loc. cit.*, vol. i, p. 171, 1903.

[154] Cushny: *Loc. cit.*, third edition, p. 629, 1899.

[155] Lewin: Deut. med. Woch., vol. xix, p. 922, 1893.

[156] Young: Brit. Med. Jour., June 13, 1903.

[157] Lancet: Nov. 26, 1898.

[158] Kraus: Deut. med. Woch., Bd. xiv, S. 227, 1888.

In the blood it is not the albuminate of mercury that does the harm, but as stated, the excess of auto-antitoxin which provokes hæmolysis. That hæmolysis affecting both the leucocytes and red corpuscles occurs under the influence of toxic doses of mercury was observed experimentally by Detre and Sellei[140] and others. Again, "the blood suffers very decidedly," says Wood,[141] "becoming more fluid and watery than normal." "According to the researches of Wright," continues the author, "its solid constituents are notably diminished, including albumin, fibrin and the red corpuscles, and it contains a large quantity of fœtid, fatty material."

Nervous Disorders.—The exaggerated proteolytic activity of the plasma, besides reducing the proportion of the blood's corpuscles, entails an untimely consumption of granulations secreted by the leucocytes, including those supplied to the neurons and the myelin throughout the entire nervous system, and to the muscular elements.* The interference with nutrition thus caused may be followed by muscular weakness, or by some form of paralysis or shaking palsy when the destructive action becomes marked. In individuals whose occupation exposes them to the constant absorption of the metal, the latter may occur before other symptoms of mercurialism, even stomatitis, appear. The muscles of the upper and lower extremities, then those of the face and tongue, are successively involved until the patient's every movement is carried out tremblingly.

The brain being likewise imperfectly nourished,* vertigo, hallucinations, insomnia and headache, and in some cases convulsions, owing to accumulation of toxic wastes, are observed. The mental phenomena are peculiar: the patient is abnormally irritable, timid and morose, melancholia ultimately developing in some instances. The senses are more or less influenced; anosmia, amblyopia and deafness being sometimes noted. Pains in the muscles, along the nerves and in the joints, and areas of anæsthesia are to be found in practically every case.

The observation of Wright, that the blood's solid constituents are notably diminished, including albumin, fibrin and the red corpuscles, has been confirmed in animals by Wilbouchewitch[142] and Hughes Bennett.[143] "Fibrin" here is obviously fibrinogen—the absence of which accounts for the fluidity of the blood and the predisposition to hæmorrhages noted in mercurialism. Wood[144] says, for instance, that "in these cases passive hemorrhages often recur again and again, and may contribute largely to a fatal issue."

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* *Author's conclusion.*

[139] Runeberg: *Ibid.*, Bd. xv, S. 4, [illegible].

[140] Detre and Sellei: Berl. klin. Woch., July 25, 1904.

[141] Wood: *Loc. cit.*, thirteenth edition, p. [illegible], 1906.

[142] Wilbouchewitch: Archives de physiol. norm. et path., Sept., 1874.

[143] Hughes Bennett: Wood, *Loc. cit.*, thirteenth edition, p. [illegible], 1906.

Charcot[145] considered trembling palsy as typical of hydrargyrism among the toxæmias of metallic origin. That, in addition to the hæmolysis previously referred to, the destruction of myelin also occurs, was emphasized by Letulle,[146] who noted absence of the sheath composed of this substance in the peripheral nerves. As it is to the reaction between the phosphorus-laden myelin and the oxygen-laden adrenoxidase of the axis-cylinder that, as I have pointed out, the formation of nerve energy is due, their functions are necessarily impaired. The axis-cylinder was found unharmed, however, by this investigator—a normal result, since, as I have shown, it contains only adrenoxidase-laden plasma. The other constituents of auto-antitoxin being absent, the adrenoxidase is harmless.

Acute Poisoning.—This is usually due to the ingestion of corrosive sublimate. When a large toxic dose of the salt has been taken, the first symptoms are usually localized in the tissues over which the poison passes, these being the seat of marked irritation or corrosion. A sharp metallic taste, a burning sensation in the mouth, pharynx, œsophagus and stomach, nausea and vomiting follow one another in more or less rapid succession, the vomited matter often containing blood. There is also violent diarrhœa with tenesmus, the stools containing shreds of mucous membrane and blood, accompanied by severe pain in the stomach and abdomen.

Sooner or later the symptoms of general poisoning appear: there is great prostration, the pulse is soft, small, rapid, and perhaps irregular, the respiration is shallow and rapid, the skin grows cold and clammy, there is almost complete anuria, the temperature is subnormal, and the patient passes rapidly into coma, dying sometimes within an hour. This constitutes the symptom-complex of excessive activity of the adrenal system and of the intense vasoconstriction (due to hypermetabolism in the vessel walls, especially the muscularis) which results. The caliber of the vessels which admit blood into the pituitary, thyroid and heart being greatly reduced, the functions of these organs are inhibited, and the vital process is arrested.*

When the quantity ingested is not very large, the gastro-intestinal symptoms occur, but the prostration fails to lapse into coma, the constriction of the arterioles being inadequate to arrest the vital functions. Within a period varying from one to twenty-four hours, therefore, the symptoms described under "*Mercurialism*" appear, including, in some cases, marked trembling. The renal symptoms are very marked, and suppression of urine may begin within a few hours (owing now to acute nephritis, in which the convoluted tubules are mainly involved) and persist to the end. In most instances the anuria disappears within twenty-four hours, but the urine is then found to contain, if the intoxication be sufficiently severe, hyaline and epithelial casts and more or less albumin. The salivation, stomatitis and glossitis are no less marked than in mercurialism. The convalescence may last several weeks, during which the patient may lose several teeth, a large quantity of hair and become considerably emaciated.

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* *Author's conclusion.*

[144] Wood: *Loc. cit.*, thirteenth edition, p. [illegible], 1906.

[145] Charcot: Mercredi méd., p. [illegible], 1892.

[146] Letulle: Arch. de physiol. norm. et path., Apr., 1887.

When the poison is introduced into the system through wounds, with the dressings, or through mucous surfaces, the vagina or rectum, by injections, the gastro-intestinal disorders appear nevertheless, but later in the history of the case, and generally along with the renal symptoms.

The corrosive action of bichloride of mercury, especially on mucous membranes, is well known. Even the skin may succumb to it. "When very strong solutions come in contact with tender parts of the skin," says Cushny,[147] "and in particular, when the salt itself is allowed to lie in contact with it for any length of time, deep corrosion, necrosis and sloughing may follow."

The process through which the other symptoms described are produced is similar to that which prevails in "mercurialism."

This identical corrosive action is that which causes the bichloride to act with greater violence than the other salts of mercury, as a toxic. Being transmitted to the test-organ by leucocytes, it is probable that it reaches this organ but slightly, if at all, modified by the auto-antitoxin in these cells, since, as observed by Stassano,[148] the sublimate in leucocytes derived from the blood of dogs poisoned with this salt, can be converted into the red iodide by appropriate treatment. Again, though as stated by Carles[149] notwithstanding the "marked resistance to the action of poisons which kill all other cells," they are themselves killed or weakened under the influence of very active poisons. In acute poisoning, therefore, the sudden invasion of the blood by the toxic endows it with almost as active irritating properties as the toxic itself. Such blood is no longer, like the albuminate, an inert agent, and its action on the adreno-thyroid center being active in proportion, so great a volume of auto-antitoxin accumulates in the blood that the vascular disorders described in the general text are produced. Hence the intense capillary hyperæmia observed in various organs, and the erythema, dermatitis, œdematous swellings, etc., to which mercurialization gives rise.

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[147] Cushny: *Loc. cit.*, p. 642.
[148] Stassano: *Loc. cit.*
[149] Carles: *Loc. cit.*, p. 85.

The treatment of poisoning by mercury is described in a special section at the end of this volume.

Therapeutics.—The beneficial effects of mercury are obtained with doses which increase sufficiently the auto-antitoxin of the blood to destroy the cause of the disease, whether it be a microörganism and its toxins or endotoxins, toxic waste products, etc.[*] When this limit is exceeded, mercury is a poison: it raises the functional activity of the adrenal center to such a pitch that the body's auto-protective system is converted into an auto-destructive system.[*]

In *syphilis,* a disease in which, owing to the mode of infection, the adrenal system is for a time inactive,[*] each case requires a given quantity to excite the test-organ, and this quantity must be carefully adjusted to the needs of the condition present, the object being to raise the immunizing potential of the blood to the degree required to destroy the pathogenic elements, but not beyond.[*]

Mercury has been used in syphilis by some clinicians on the general principle that the quantity introduced into the system would antagonize a correspondingly active morbid process.[*] Being a formidable malady, it is thought that "a greater impression is made on the disease"—using the words of a recent writer—when large quantities are administered by inunctions, subcutaneously, etc. As will be shown, this is quite unnecessary and may prove very harmful.

Owing to the external use of mercurial preparations as antiseptics, the belief that they might act similarly in *biliousness, gastro-enteritis, summer diarrhœa,* etc., has caused them to be tried, and, in many instances, with gratifying results. These should not be attributed to a direct action of the preparations used, but to their influence on the test-organ, and to the bacteriolytic and antitoxic action of the blood's auto-antitoxin, the production of which they promote.[*] By enhancing metabolism, small doses have likewise proven valuable in *anæmia, sthenic inflammation,* and kindred disorders.

This is well shown in the condition known as "*biliousness,*" due to hypocatabolism of physiological toxic wastes; 10 grains (0.66 gm.) of blue mass, followed by a saline aperient to remove any excess of the drug in the intestine, promptly corrects this disorder by stimulating the body's auto-protective mechanism. Such a large dose is not needed, however, to insure this action: $^1/_{10}$ grain (0.0065 gm.) of calomel with a little soda bicarbonate every hour, five times, will act as efficiently, since a minute dose suffices to excite the test-organ. If flushing of the intestine is desired, *i.e.*, a copious flow of antitoxic intestinal juice in addition to the hepatic action, larger doses: $^1/_6$ to $^1/_2$ grain (0.01 to 0.03 gm.) every 15 or 30 minutes until 1 or 2 grains (0.065 to 0.1 gm.) are taken, may be ordered. In the *gastro-enteritis* due to the presence of fermentative toxic products of digestion $^1/_{50}$ to $^1/_{60}$ grain (0.0013 to 0.001 gm.) doses of the yellow oxide in sugar of milk, or in the *summer diarrhœa* $^1/_{50}$ grain (0.C0013 gm.) of the bichloride every hour in solution until relief is obtained, are very effective through a similar process. In *gastric irritation* from the same cause, or where there is also *vomiting*, either in adults or children, $^1/_{100}$ grain (0.00065 gm.) of the bichloride is often curative given every hour five times, then at longer intervals; provided, of course, dietetic errors be corrected. In *gastric ulcer* $^1/_{60}$ to $^1/_{50}$ of the bichloride before meals promotes cicatrization of the ulcers.

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[*] *Author's conclusion.*

To increase the nutrition in *asthma*, especially in children in whom the stools are pasty and ill-smelling, $^1/_{60}$ grain (0.001 gm.) given every hour five times, and repeated at one week's interval, is very beneficial. The powder may be mixed with a little sugar and applied to the tongue. In *anæmia* $^1/_{60}$ to $^1/_{40}$ grain (0.001 to 0.0016 gm.) of the bichloride three times daily is of recognized value. Mercurials were long in favor to counteract *sthenic inflammation*, but, except in iritis due to syphilis, are now seldom employed. The use of excessive doses accounts for this fact, very small doses alone being indicated.

The bacteriolytic and antitoxic activity which the blood and the intestinal juices acquire under the influence of mercurials, accounts for the beneficial effects observed in various infectious diseases, *typhoid fever, diphtheria, acute tonsillitis, puerperal septicæmia, etc.*

In *typhoid fever* German practitioners give 10 grains (0.66 gm.) of calomel daily for three days. Others have also found that small doses, $^1/_{10}$ grain (0.0065 gm.), four times in the twenty-four hours diminished considerably the intensity of the disease and its duration. The Germans regard the drug as an antipyretic, owing to the effects observed. In the light of my views the reduction of the temperature is due to the fact that the pathogenic organisms and their toxins are greatly reduced through the increased activity of all immunizing processes. Among others, Rondot[130] observed a decided shortening of the disease in 21 cases, and diminution of the severity of the symptoms by the use of $^1/_{12}$ grain (0.005 gm.) of bichloride daily, divided in very small doses given at short intervals.

Ackley[131] found that a mixture of $^1/_{12}$ to $^1/_{10}$ grain (0.005 to 0.0065 gm.) of the biniodide and 10 grains (0.66 gm.) of saccharated pepsin every six hours checked the marked symptoms and greatly shortened the duration of the disease.

Before antitoxin—which should always be given the preference when available—was introduced, one of the most effective agents in *diphtheria* was calomel in large doses. The cyanide, $^1/_{100}$ to $^1/_{50}$ grain (0.00065 to 0.0013 gm.), every hour, or the bichloride, $^1/_{40}$ to $^1/_{10}$ grain (0.0016 to 0.0065 gm.), can be given one or two days, even to children, with less danger of causing salivation. The simultaneous use of depressing drugs should be avoided.

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[130] Rondot: Gaz. heb. des Sci. méd.; Boston Med. and Surg. Jour., Feb. 28, 1889.

[131] Ackley: Pittsburgh Med. Rev., June, 1890.

Daly[152] recommended Reiter's method: 2 to 5 grains (0.13 to 0.3 gm.) of calomel every hour until the stools acquire a greenish hue, when the intervals are lengthened. Selldén[153] reported 1400 cases treated by colleagues and himself with the cyanide of mercury, in which the mortality was only 4.9 per cent. A teaspoonful of a 1 in 10,000 solution was given every half to one hour, according to the age of the child. The importance of avoiding other drugs is that various agents that have been tried in diphtheria tend to depress the protective functions.

Among other disorders distinctly influenced by mercurials owing to the increase of immunizing substances their use provokes, are *acute tonsillitis*, *puerperal septicæmia*, the *exanthemata* of childhood, and *cerebro-spinal meningitis*.

IODINE AND THE IODIDES.

Physiological Action.—Iodine and its preparations, in whatever way administered, are taken up by the leucocytes, and it is through the intermediary of these cells that they—or rather the substances into which the leucocytes convert them—penetrate into the circulation. The thyroid and parathyroid glands being the organs which utilize iodine for the elaboration of their secretion, thyroidase, all the iodine ingested with foods is distributed to these glands. When iodine or its preparations are administered, however, these organs do not necessarily utilize the quantity ingested; as iodine is one of the substances which the body stores for future use, they admit only enough blood (and, therefore, iodine-laden leucocytes) to supply their momentary need.*[154] As a result, the thyroidase cannot become overrich in iodine; its sensitizing influence on all the cellular elements of the body, including those of the pituitary, and its stimulating action on the test-organ of the latter are always the same under normal conditions.* If from any cause, however, the food fails to supply enough iodine to satisfy the needs of the thyroid apparatus, therapeutic doses of this halogen prove beneficial through this apparatus, by enabling it to restore to the blood what proportion of thyroidase it may be lacking.*

The main therapeutic action of iodine and its preparations, however, is of another kind. It is due to the direct action of the iodine compound (secreted by the leucocytes which have failed to be admitted in the thyroid and parathyroid) upon the test-organ and stimulation of the latter.* As this causes overactivity of the adrenals and a corresponding increase of adrenoxidase in the blood, general metabolism becomes more active. As a result, nutrition is improved, the processes of repair are hastened, and the bacteriolytic and antitoxic powers of the blood are greatly enhanced.*

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* *Author's conclusion.*

[152] Daly: "Trans. Amer. Laryn. Assoc.," vol. viii, p. 73, 1886.

[153] Selldén: Wiener med. Presse, Bd. xxix, S. 522, 1888.

[154] *Cf.* this vol., p. 1067 *et seq.*

Therapeutic doses of iodine, or its salts, do not cause emaciation, and do not influence either the blood-pressure or the pulse.

The manner in which iodine is taken up by the leucocytes in the intestinal canal and the blood; the relationship between these cells and the thyroid apparatus, and, finally, the mode of action of the iodine-laden secretion of the latter on the test-organ, were treated in the preceding chapter.

As to the influence of iodine upon metabolism, Nothnagel and Rossbach,[155] alluding to the effects of the iodides on nutrition, write: "During a certain period the conviction that iodine and potassium iodide produced emaciation was such that all the theories on the mode of action of iodine were based on that idea. But this view has been actively combatted (Ricord, Boinet, Wunderlich), and it was finally concluded that K I not only did not cause emaciation, but that, conversely, it caused fattening." In truth, both views are sound. As stated by Manquat:[156] "Emaciation is an inconstant symptom, it is true, but it is often witnessed, especially with larger doses than 2 gms. (30 grains) daily. With very small doses (0.25 gm.—4 grains) it is not only not to be feared, but there occurs greater activity of the circulation, and secondarily of the nutrition, particularly of the myocardium." In other words, large doses produce emaciation and small doses enhance nutrition. This corresponds with the apparently contradictory results as to the excretion of nitrogenous and other wastes: While Rabuteau, Milanesi and Bouchard,[157] Henrijean and Corin,[158] and others, noted an increase of nitrogen output, Handfield Jones,[159] in a series of six cases, noted an increase in only three patients, while the other three showed a decrease—all taking large doses of potassium iodide.

All these discordant observations assume a normal aspect in the light of my views: when the doses are small the test-organ is stimulated just enough to enhance nutrition, while large doses, by stimulating it too actively, excite hypermetabolism, *i.e.*, excessive consumption of tissue elements and wasting. That such is the case is further shown by the fact referred to by Wood[160] and Cushny,[161] that iodine sometimes causes fever.

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* *Author's conclusion.*

[155] Nothnagel and Rossbach: "Mat. médicale et thérap.," sixth edition, p. 370, 1889.

[156] Manquat: "Thérapeutique," vol. ii, p. 100, 1903.

[157] Bouchard: C. r. de la Soc. de biol., pp. 227, 237, 1872.

[158] Henrijean and Corin: Arch. de Pharmacodyn., T. ii, 1896.

[159] Handfield Jones: Beale's Arch., vol. i, cited by Wood: "Therapeutics," thirteenth edition, p. 502, 1906.

[160] Wood: "Therapeutics," thirteenth edition, p. 490, 1906.

[161] Cushny: "Pharmacol. and Therap.," fourth edition, p. 514, 1906.

"Though we ascribe to it alterative virtues," says Griffin,[162] "we are thereby not much nearer an understanding of its action, though some pronounced action over nutrition and its disorders it certainly does possess."

As hypermetabolism involves the presence in the blood of an excess of auto-antitoxin, the blood's bacteriolytic and antitoxic efficiency is increased in proportion. It is likewise richer in phagocytes, as shown by Heinz[163] and Schleich.[164] So active, in fact, can the blood become as an immunizing agent that excessive doses can provoke hæmolysis. Thus Henrijean and Corin found that 1 gm. (15 grains) of sodium iodide reduced the red corpuscles from 6,250,000 to 4,125,000 in the rabbit, in twenty-four hours. Heile also observed that iodoform caused autolysis.

Therapeutic doses of iodine or of its preparations do not influence the blood-pressure or the pulse. Stockman and Charteris[165] state that, although ordinary doses of sodium or potassium iodide cause no change in the strength or rapidity of the pulse, "reference to text-books on pharmacology and therapeutics shows that most authors attribute to the iodides a depressing effect on the circulation and blood-pressure, while only a minority hold that there is no adequate proof of this." Using von Basch's sphygmomanometer and Gärtner's tonometer, they studied the blood-tension and pulse-rate of numerous patients who, for one reason or another, were taking potassium or sodium iodide. Although the doses taken ranged from 15 to 180 grains (1 to 12 gms.)—one, in fact, 300 grains (20 gms.)—daily, "in no case did any fall in the blood-pressure occur, or any change in the rhythm of the heart." Similar researches were undertaken by James Burnet[166] in a variety of cases, including aneurism, arteriosclerosis, angina pectoris, asthma and tertiary syphilis, potassium iodide being given by the mouth. He observed "no effect whatever, either upon the pulse-rate or blood-pressure within the arteries." The hypodermic use of iodipin was also studied. "In no case," says the author, "was the blood-pressure altered; nor was the heart's rate or rhythm affected. Especially, I found that the heart's action was never increased nor depressed, and that the pressure within the radial artery, when markedly high to begin with, was never lowered, even after a prolonged use of the iodipin injections. Still, all the same, I had good results in nearly all my cases."

Iodine and its preparations not only do not, as shown above, cause vasodilation either in large or small doses, but they provoke constriction of all vessels, arteries and veins, because these vessels are supplied with a muscular coat, and owing to the excessive metabolism which they incite indirectly in this, the contractile layer of these vessels.* This morbid phenomenon is aggravated by another factor: the presence in the blood of sufficient iodine to irritate the intima, a feature which, in itself, tends to promote constriction in vessels supplied with vasomotor nerves. What has been mistaken for general vasodilation is dilation of the capillaries.* These

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* *Author's conclusion.*

[162] Griffin: Foster's "Therapeutics," vol. I, p. 535.

[163] Heinz: Virchow's Archiv, Bd. clv, S. 44, 1899.

[164] Schleich: Cited by Manquat: *Loc. cit.*, p. 101.

[165] Stockman and Charteris: Brit. Med. Jour., Nov. 23, 1901.

[166] James Burnet: Medical Mag., June, July, 1904.

delicate vessels not being supplied with a muscular coat or vasomotor nerves, are not morbidly influenced as are the others,* but they suffer indirectly: the arteries and veins, by contracting inordinately, drive the blood into them and cause *passive* dilation.* So great is the pressure in some cases, that the plasma is forced out of the capillary walls in relatively large quantities—sufficient, in fact, to cause œdema of the face, larynx, pleura, lungs, etc., and even to provoke their rupture, as shown by the ecchymosis, hæmorrhages, hæmaturia, purpura, menorrhagia, metrorrhagia, etc., witnessed.

E. Cyon[167] also lays stress on the fact that it is a grave error to consider iodine as a vasodepressor. The prevailing view that iodine and its preparations lower the blood-pressure is due to a deplorable habit (deplorable in the sense that it has contributed greatly to obscure our knowledge of the action of all drugs) into which experimenters have fallen, of taking as standard the poisonous effects of a remedy for its therapeutic action. Thus I have before me the protocol of experiments by an eminent therapeutist in which 0.25 gm. ($3^9/_{10}$ grains) per kilo of animal are administered to rabbits to illustrate the therapeutic action of potassium iodide. An equivalent dose to an average adult (70 kilos) would thus be 17.5 gms. (270 grains). Of course, he obtained vasodilation in five minutes—but dilation of the capillaries only, as we will see. Now, Sée and Lapicque[168] found that certain proportions of the various iodides per kilo of animal were necessary to produce such vasodilator effects. Adapting their figures (the first column) to an adult of 70 kilos, the proportions used by the unnamed investigator to exemplify the therapeutic action of the drug, would be those given in the second column:—

	Example of experimental "therapeutic" dose in animals.	Equivalent of supposed "therapeutic" dose in adult man.
Iodide of Sodium	0.32 gm.	22.4 gms. = 346 grains
Iodide of Sodium	0.30 "	21. " = 324 "
Iodide of Strontium	0.32 "	22.4 " = 346 "
Iodide of Calcium	0.24 "	16.8 " = 259 "
Iodide of Potassium	0.27 "	18.9 " = 291 "
Iodide of Potassium	0.23 "	16.1 " = 248 "

Such a dose, suddenly thrown into the circulation, in no way illustrates the mode of action of iodine preparations used therapeutically, especially when administered orally—not even when large quantities are given. Prévost and Binet[169] and others who have observed "vasodilation" specify, moreover, that it was produced by large doses.

As to the irritating influence of iodine (accumulated in the blood) on living elements, it is not only exemplified by the irritating action of iodine on the skin and mucous membranes, but also by the irritation attending its elimination through the skin, kidneys, etc. As to its influence on vessels, von Zeissl[170] found that when iodine was injected into the carotid of dogs, the blood-pressure rose intensely, producing œdema not only of the brain, but also of the lungs. This is ascribed to a direct action on the vessels. Although violent stimulation of the test-organ doubtless assisted in provoking such excessive vasoconstriction, the fact remains that the local irritation contributed materially as cause. The production of excessive vasoconstriction is well shown by a case of fatal poisoning following the injection into an ovarian cyst, reported by Rose.[171] At the autopsy he found that even comparatively large *arteries* were completely occluded. Bogolopoff,[172] on the other hand, observed microscopically that in frogs, into which a solution of potassium iodide had been injected, the *capillaries* were markedly dilated.

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* *Author's conclusion.*

[167] E. Cyon: "Les Nerfs du Cœur," Paris, 1905.

[168] Sée and Lapicque: Bull. de l'Acad. de méd., T. xxii, p. 238, 1889.

[169] Prévost and Binet: Rev. méd. de la Suisse Romande, vol. x, p. 509, 1890.

The production of œdema and interstitial hæmorrhage could be illustrated by a large number of cases on record. In a case reported by Milian,[173] for example, 6 gms. (90 grains) daily brought on at the end of six days, an ecchymosis and large submucous hæmorrhage of the palate. Wallace[174] observed pleural exudation and pulmonary œdema after prolonged treatment. Œdema of the glottis may be brought on by 45-grain (3 gm.) doses (Fenwick), or much larger doses; but smaller doses have also caused it: 15 grains (1 gm.) in cases reported by Nélaton, Fournier, Huchard, Rosenberg; or small doses in cases reported by Fournier, La Barcerie and Guillemet. In all these cases, of course, the remedy had been used during a more or less prolonged period. The brain may also become hyperæmic. Sokolowski,[175] in animals trephined after the administration of large doses of potassium iodide, found the cerebrum gorged with blood. This accounts for the observation of Rilliet that iodine could cause a sort of drunkenness attended with excitement, tinnitus, palpitations and even convulsions, and for the cases of cerebral hæmorrhage reported by Hallopeau.[176] This excessive vasoconstriction may even entail death, as in a case observed by Franz,[177] in which 1 gm. (15 grains) doses led to acne, ulceration of the nares, abscesses, etc., and finally death by double hydrothorax and pulmonary œdema.

Iodism.—This condition is due to the presence of an excess of iodine in the blood over and above the aggregate of this halogen required by the body at large.* This aggregate is represented by the iodine contained in the thyroid and parathyroids, the red corpuscles (which take up their thyroidase) and what reserve the body fluids and the different organs can accommodate.

Although, on the whole, large quantities of iodine or its salts, whether given in one dose or in many small doses, are more likely to cause iodism than small quantities, the question of dose is subsidiary to the condition of the patient. A very small quantity may thus produce iodism merely because the patient's asset in iodine is up to its maximum limit*—his supposed "iodiosyncrasy."* This is particularly the case in subjects whose thyroid apparatus is only able, owing to local disorders (goiter, for example) or deficient development, to take up a small proportion of this halogen.* Any condition which inhibits more or less its excretion also predisposes a patient to iodism, by causing his asset to remain high.*

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* *Author's conclusion.*

[170] von Zeissl: Zeit. f. klin. Med., Bd. xxvii, S. 263, 1895.

[171] Rose: Virchow's Archiv, Bd. xxxv, S. 12, 1866.

[172] Bogolopoff: Arbeit. a. d. pharm. Labor. z. Moskau, S. 125, 1876; Revue des Sci. méd., vol. x, p. 92, 1877.

[173] Milian: Presse méd., Sept. 30, 1899.

[174] Wallace: Cited by Nothnagel and Rossbach: *Loc. cit.*, p. 270.

[175] Sokolowski: *Ibid.*, p. 269.

[176] Hallopeau: Cited by Manquat: *Loc. cit.*, vol. ii, p. 94.

[177] Franz: Wien. klin. Woch., Bd. xii, S. 642, 1899.

The two physiological effects of iodine on the test-organ (the direct action plus the sensitizing action of the thyroidase which acquires its *normal* (but not maximum) power during the use of iodine) causing it to react violently, the adrenals are stimulated with corresponding vigor and, the excess of iodine in the blood aiding, abnormal vasoconstriction, produced in the manner described, occurs. This abnormal vasoconstriction is the direct factor in the production of iodism, and may give rise to four classes of morbid phenomena: (1) passive engorgement or congestion of all capillaries; (2) œdema, when the engorgement becomes excessive; (3) ecchymoses and hæmorrhages when the walls of the capillaries are ruptured; and (4) arrest of function and nutrition when the vasoconstriction is such as to reduce or arrest the flow of blood to the tissues.

The group of morbid phenomena due to capillary engorgement includes:* in the respiratory tract, coryza, antral and frontal pain, pharyngitis, tonsillitis, cough, hoarseness, tracheobronchitis and pulmonary congestion; in the nervous system, headache, insomnia, delirium, neuralgia, neuritis, pleurodynia; in the muscular system, myalgia, tremor, twitching and spasm (the spinal centers being likewise hyperæmic); in the organs of special sense, conjunctivitis, dacryocystitis, tinnitus aurium, deafness, perversions of taste; in the digestive system, gastric irritation, vomiting and diarrhœa; in the skin, pruritus, erythema and dermatitis; in the urinary system, polyuria, albuminuria and nephritis; in the glandular organs, salivation, parotitis and hepatitis with icterus. Less frequently seen are the œdematous infiltrations: œdema of the larynx, palate, pleura and lungs, and of the lids, lips, neck, and even the entire surface. Rupture of the capillaries under the stress of the blood-pressure is denoted by more or less extensive ecchymoses sometimes involving large areas, epistaxis, hæmoptysis, hæmaturia, menorrhagia and hæmorrhagic purpura.

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* *Author's conclusion.*

The fourth group, due to excessive initial vasoconstriction, thus obliterating or reducing more or less local blood-supply and depressing functional activity,* includes as to the brain, somnolence, intellectual torpor, vertigo, loss of memory, hebetude, hypochondria, and melancholia; as to the spinal system and muscles, adynamia, muscular flaccidity, incoördination, paralyses, a sensation of weight in the limbs; as to the alimentary canal, constipation; as to the skin, cyanosis, ulceration and necrosis. Nutrition may thus be impaired sufficiently under the prolonged use of iodides to produce atrophy, especially of the mammæ and testicles.

Cutaneous eruptions of various kinds, papular, vesicular, eczematous, erysipelatous, pustular, etc., may appear during the administration of iodine or its salts, especially of the potassium iodide. The presence of several of these eruptions coincides with that of other symptoms of iodism and with abnormal vasoconstriction; they are due to the fact that the latter condition, by causing retention of the drug in the capillaries of the skin, promotes therein disorders similar to those produced by external applications of iodine. The multiplicity of cutaneous disorders is due to the presence in these capillaries of different kinds of wastes: alloxuric bases, hypocatabolized cellular débris, various acids, etc., each of which affects the cutaneous elements in its own way. The underlying cause of all these eruptions, therefore, is the same as in all phenomena witnessed in iodism, viz., abnormal vasoconstriction.*

All these phenomena, and the excessive constriction of the arteries, would not occur were iodine able to excite the thyropressor nerve.* But such is not the case. Even when taken in doses sufficient to produce acute poisoning, iodine and its preparations fail to increase the secretory activity of the thyroid.* Were it, in fact, otherwise, this organ would waste its product whenever its own pabulum, iodine, would enter the blood.*

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* *Author's conclusion.*

That retention of iodine must prove deterimental is suggested by the proportion eliminated. In a case treated by H. C. Wood[178] 265 grains (17 gms.) were recovered daily by Marshall from the urine alone, out of 360 grains (24 gms.) administered. According to Wood, "Sée states that the elimination is apt to be irregular, so that the drug may accumulate in the system." Cushny[179] says, moreover, that among the conditions "which favor the onset of symptoms, is a slow excretion of the iodine such as is observed in some forms of renal irritation."

As to the quantities of iodine or its salts which produce iodism, the comprehensive research of Briquet[180] in several hundred cases, led to the conclusion that "the greater the dose of any iodide, the greater the likelihood that iodism will appear, and that the symptoms will be severe"—contrary to the prevailing opinion. He cites, moreover, cases reported by Bresgen, Nègre and Petitjean in which large doses would produce it, while smaller doses would not. According to my own interpretation of its effects, the nearer the patient's condition approximates normal health, the greater are the chances of his developing iodism. I have not only observed this fact clinically, but Ricord, Jullien and Wood, according to Briquet, have observed that syphilitics appear, on the whole, to be practically immune to the morbid effects of the iodides as compared to others. There is no doubt, moreover, that very small doses can produce iodism in accord with the prevailing view. In one of my goitrous cases, less than 1 minim (0.065 c.c.) of the tincture of iodine daily produced it; Rilliet[181] observed that even sea-air and cod-liver oil sufficed to awaken morbid phenomena in these cases. Gautier[182] confirmed the observation as to the influence of the sea-shore, and refers to a case in which poisoning followed "the application of iodine dressing to a tooth by a dentist." The reason for this becomes self-evident if interpreted from my standpoint. While Baumann[183] found that the amount of iodine in the thyroid was greatly reduced when this organ was diseased, Ewald[184] observed that in advanced colloid degeneration of the gland only traces of iodine were present. The loss of the body's great storehouse for this halogen accounts for its accumulation in the blood and the readiness with which morbid phenomena are produced. This indicates how the organism resents even minute quantities when they exceed the physiological limit. Indeed, irrespective of the presence of goiter, small doses may also provoke iodism. Hynes[185] reported a case in which 3-grain (0.2 gm.) doses brought on hæmorrhagic rash; and H. C. Wood[186] one in which 6 grains (0.4 gm.) daily brought on violent conjunctivitis with facial œdema.

The presence of iodine in the cutaneous secretions has been shown by R. W. Taylor,[187] and other observers have found it in the saliva, nasal secretion, milk, etc. Its morbid influence in the production of the cutaneous disorders during elimination is generally recognized. Cushny[188] writes: "That a similar action on the skin may be induced by iodine and iodides is shown by the application of iodine to the skin, being often followed by eruptions which are not confined to the point of application, but spread." That toxic wastes must be retained as well as the iodides in the cutaneous capillaries hardly needs to be emphasized; their influence in the pathogenesis of eruptions is also well-known.

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[178] H. C. Wood: *Loc. cit.*, thirteenth edition, p. 490, 1906.
[179] Cushny: *Loc. cit.*, fourth edition, p. 508, 1906.
[180] Briquet: Semaine méd., vol. xvi, p. 137, 1896.
[181] Rilliet: Cited by Nothnagel and Rossbach: *Loc. cit.*
[182] Gautier: Rev. méd. de la Suisse Rom., vol. xix, p. 613, 1899.
[183] Baumann: *Loc. cit.*
[184] Ewald: *Loc. cit.*
[185] Hynes: Lancet, Feb. 13, 1904.
[186] H. C. Wood: *Loc. cit.*, thirteenth edition, p. 501, 1906.
[187] R. W. Taylor: Amer. Jour. of Syphilis and Derm., vol. iv, p. 119, 1873.
[188] Cushny: *Loc. cit.*, fourth edition, p. 506, 1906.

The list of symptoms observed in iodism could be considerably lengthened—sufficiently so, in fact, to show that the three degrees of passive capillary hyperæmia: the simple, exudative and hæmorrhagic, can be provoked by iodine and its preparations in *all* organs. The fact that such an array of phenomena can be explained by this one general mechanism, affords in itself conclusive proof of its soundness as an explanation of iodism—especially in view of the fact that the physiological action of iodine has remained unknown.

Acute Poisoning.—When a poisonous dose of iodine is taken, a sense of severe burning in the pharynx and œsophagus is soon followed by nausea, retching and vomiting, and ultimately by cramps and, in some cases, purging. These are purely local phenomena due to the caustic action of the drug.

When a large quantity of iodine passes into the blood, the general vasoconstriction, described in the preceding pages, becomes such that all functions are inhibited, including those of the heart, owing to narrowing of the coronaries and other cardiac arteries.* The heart-walls being no longer supplied with enough blood to sustain their functional activity,* their contractions weaken, and the pulse becomes frequent, feeble and thready. This condition is aggravated by the concomitant constriction of the arterioles which supply the pituitary body and the inhibition of all the functions carried on by this organ.* Great weakness, anuria and cyanosis appear and death occurs from heart-failure. If the patient survives, the acute vasoconstriction of the arterioles becomes less marked, and the blood, driven to the periphery by the contracted central vessels, floods the superficial capillaries,* causing marked flushing and even blotches resembling exanthematous patches, hæmorrhages, etc., though the temperature remain low. If death does not occur, the acute symptoms may be replaced by those of iodism and the patient lingers for some time, dying more or less suddenly of cardiac inhibition.* Recovery occurs in a large proportion of cases, however, when the dose taken is not excessively large.

The morbid process in acute poisoning differs from that of the fourth group of "iodism" only in that the hyperconstriction comes suddenly and with probably greater violence. I have shown elsewhere[illegible] that the belief of physiologists that the coronaries are not supplied with vasomotor nerves is erroneous. This question is reviewed in a succeeding chapter, where a microphotograph shows beyond question the existence of such nerves. All the arteries of the body being constricted simultaneously, the caliber of the arteries of the pituitary is not reduced as greatly as it is when their contraction is due to depressor impulses. The morbid effects on the other organs, the heart, for instance, stand out, therefore, more prominently. The secondary hyperæmia, exanthematous patches, etc., referred to have been observed by several clinicians to follow acute poisoning.

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* *Author's conclusion.*

[illegible] New York Med. Jour., May 14, 21, 1904.

The *treatment of poisoning by iodine* is described in a special section at the end of this volume.

Therapeutics.—The foregoing interpretation of the physiological action of iodine and the iodides accounts for their marked value in diseases characterized by impaired metabolism, defective nutrition, certain infections and chronic inflammatory process in which resolution is delayed. In *gout, rheumatism, asthma* and disorders of the *menopause*, their beneficial effects are due to the fact that by increasing the autoantitoxin in the blood, the pathogenic toxic wastes are not allowed to accumulate. In *syphilis, tuberculosis* and *scrofula*, their power to promote phagocytosis also comes into play, the bacteria, their toxins or endotoxins, being combatted by the same constituent—antitoxic and bacteriolytic—which is caused to accumulate by injections of tuberculin or kindered substances. Even parasites may be destroyed by the digestive activity which the blood acquires through iodine and its salts, as shown by its remarkable effects in *actinomycosis*. In torpid processes, such as *chronic bronchitis, pleuritis* or *endocarditis*, the curative action of these valuable agents differs in no way from the above: by increasing the activity of metabolism, they promote nutrition and process of repair, while simultaneously insuring the destruction of the detritus and of any pathogenic germ that may be present—all this, while protecting the body against renewed infection.*

The doses indicated differ in each case, since its action is dependent upon the asset of the organism and the condition of the test-organ. If the patient's asset is up to the maximum, as is often the case in normal subjects, small doses suffice to raise the functional activity of the test-organ and, therefore, the defensive properties to a high degree of efficiency.* If conversely his asset is small, his thyroid poor in iodine-laden cells, and his test-organ is torpid, conditions essentially present in syphilis and various disorders accompanied by paralysis,* large doses are necessary, first to replenish the thyroid and enable it in turn to supply the red corpuscles and all cells with enough thyroidase to endow them with the normal irritability, and second to awaken the test-organ from its lethargy.*

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* *Author's conclusion.*

ADRENAL EXTRACTIVES.

(Adrenal Extract, Adrenalin, Epinephrin, Suprarenalin, etc.)

Physiological Action.—When a therapeutic dose of an adrenal active principle, adrenalin, epinephrin, etc., or that embodied in adrenal extract, is introduced directly into the blood, it increases, in proportion to the quantity administered, the catalytic and oxygenizing properties of the hæmoglobin, and the activity of cellular interchanges—the vital process itself—is thus enhanced.* This effect is shown prominently in conditions such as surgical shock in which all functions are markedly depressed.

The influence of the drug on metabolism is well shown by the rise of temperature it causes. Reichert[180] observed that adrenal extract caused an elevation of 1° F. in rabbits, accompanied by increased metabolic activity. Lépine[181] states that the increase of blood-pressure caused by adrenal extract is always followed by a rise of temperature. Morel[182] noted that it caused in guinea-pigs a rise of from 0.9° to 1.8° F. Again, Kinnaman,[183] in a comprehensive study of the temperature relationship to shock, concluded that as shock increased in severity, the most uniform and progressive factor was the fall in temperature. He states that "in one series [of cases] the fall in temperature was the sole cause of shock." The results of Crile[184] with adrenalin in salt-solution given very slowly and gradually for a considerable time thus find a normal explanation. He supplied the organism precisely with the substance which sustains the vital process in the tissue cells. He also resuscitated animals in this manner—with simultaneous artificial respiration—fifteen minutes after all signs of life had ceased, and was able to keep a decapitated dog alive over ten hours by this same procedure.

By enhancing the catalytic and oxygenizing properties of the blood, and therefore tissue metabolism, adrenal extractives provoke directly effects that are produced indirectly through the adrenals, by drugs and poisons capable of stimulating the test-organ.* The functional activity of all organs—including the leucocytogenic structures and the pancreas—being enhanced, the blood is provided with an increase of phagocytes and of plasmatic auto-antitoxin.* Adrenal extractives thus increase the immunizing properties of the blood.

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* *Author's conclusion.*

[180] Reichert: Univ. of Penna. Med. Bull., Apr., 1901.

[181] Lépine: Semaine méd., Feb. 18, p. 53, 1902.

[182] Morel: Le progrès méd., Aug. 2, 1902.

[183] Kinnaman: Annals of Surgery, Dec., 1902.

[184] Crile: Boston Med. and Surg. Jour., Mar. 3, 1903.

Byelaventz[235] found experimentally that adrenalin first increased the gaseous interchanges. This shows that it becomes an inherent factor of the blood's oxygenizing constituent. This action is evidently widespread, for Ioteyko[236] noted that adrenalin increased markedly the contractility of muscles under electrical excitation. Battelli, moreover, found that during fatigue the proportion of adrenalin in the adrenals was diminished, while conversely Dessy and Grandis[237] observed that an aqueous solution of adrenal extract injected into the exhausted animal restored the contractility of its muscles in from 2 to 8 minutes, and rendered them more resistant than before the experiment.

That the adrenals cause, in some way, the destruction of blood-poisons has asserted itself so prominently that various investigators, Abelous and Langlois,[238] for example, consider it as their only function. This is the basis of the so-called "auto-intoxication" theory. Indeed, these investigators, and also Albanese, having observed that animals deprived of their adrenals rapidly succumbed to a short exertion, they concluded that it was the secretion of the adrenals which neutralized the muscular toxic wastes. This theory has failed in its main feature, however, for there is no foundation for the belief that the secretion itself destroys these poisons. Interpreted from my standpoint, Abelous and Langlois's theory assumes another aspect: the adrenal secretion being, as adrenoxidase, a constituent of the bacteriolytic and antitoxic triad trypsin, and the one which endows it with its quality as a ferment, the antitoxic power of the blood gradually diminishes after extirpation of the adrenals (since the animal lives a short time on what adrenoxidase his blood happens to contain), and the muscular toxic wastes being less and less destroyed, accumulate in the blood. Hence the fact that exertion after removal of the adrenals hastens, as we have seen, the lethal issue, while the post-operative use of adrenal extract, as first shown by Brown-Séquard,[239] prolongs life. Schäfer[240] states, moreover, that "the transfusion of normal blood into the veins of 'decapsuled' animals tends markedly to prolong their survival of the operation." In other words, in whatever form the active principle of the adrenal secretion is introduced, it increases the antitoxic power of the blood—precisely as is the case when the test-organ is stimulated by a poison. The digestive (antitoxic) power of the blood—including phagocytosis—may be so increased, in fact, that destruction of the blood-cells themselves will occur. Thus Loeper and Crouzon[241] observed that injections of adrenalin into the blood first caused leucocytosis, then hæmolysis. Nor does this apply only to toxic muscular wastes, for Meltzer and Auer[242] found that the intravenous injection of adrenalin renders a rabbit resistant to a surely fatal dose of strychnine.

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* *Author's conclusion.*

[235] Byelaventz: Russkii Vratch, vol. ii, No. 7, 1903.

[236] Ioteyko: Jour. de méd. de Bruxelles, July 9, 16, 23, 1903.

[237] Dessy and Grandis: Arch. Ital. de Biol., May 31, 1904.

[238] Abelous and Langlois: C. r. de la Soc. de biol., p. 855, 1891; p. 388, 1892; p. 444, 1893.

[239] Brown-Séquard: C. r. de la Soc. de biol., T. xliv, p. 410, 1892.

[240] Schäfer: "T. B. of Physiol.," vol. i, p. 948, 1898.

[241] Loeper and Crouzon: Arch. de méd. exper., vol. xvi, p. 83, 1904.

[242] Meltzer and Auer: Med. News, June 4, 1904.

When applied locally to mucous membranes, adrenal extractives produce blanching through local ischæmia. This is due to the fact that they excite very active local metabolism in all the tissues into which they penetrate.* The muscular elements of the arterioles and veins being thus caused to contract to their utmost limit, the access of blood to the cellular elements is prevented.* The energetic consumption of cellular materials which this excessive constriction entails,* is sometimes sufficient to cause gangrene by arresting local nutrition. Again, it leaves the cellular elements deprived of nutrient materials for a time,* their restoration occurring in a measure according to the age and general recuperative activity of the patient. Hence* the gaping vessels, the œdematous infiltration, etc., observed after the local use of adrenal extractives, especially in debilitated and aged subjects, and the post-operative hæmorrhages occasionally witnessed.

Local hypermetabolism is well exemplified by the experiments of Herter and Wakeman,[303] in which they found that by painting the pancreas with 1 c.c. of a 1 in 1000 solution of adrenalin, they caused glycosuria. In the light of my interpretation the solution increased markedly the functional activity of the pancreas, and increased the production of amylopsin—the ferment which converts glycogen into sugar. Wolownik-Charkow[304] found that after the administration of large doses to rabbits, the liver contained less glycogen than the control animal. Müller[305] found, moreover, that adrenal extractives produced no morbid changes in the tissues—thus pointing to mere excess of activity—and that it did not interfere with reparative changes.

So intense is this local vasoconstriction that Braun[306] found that a solution of 1 in 1,000,000 of the active principle depleted the tissues as if they had been frozen. Neugebauer[307] and others have, in fact, found that it caused gangrene, the tissues being totally deprived of blood. Taramasio[308] observed a similar effect in experimental animals. This illustrates the activity of the intracellular exchanges it provokes in the muscular elements of the vessels, and for the observations of F. E. Hopkins,[309] Kyle[310] and others, that its use is liable to be followed by post-operative hæmorrhage, the vessels being left gaping when the action of the extractive passes off. Seitz[311] observed sloughing of the nasal tissues. Solomon Solis-Cohen[312] reported an instance of acute œdema of the uvula, palate, pharynx and epiglottis. A similar, though more extended œdema, occurred in a case treated by Bloch.[313] Many instances of this kind have been reported.

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* *Author's conclusion.*

[303] Herter and Wakeman: Amer. Jour. Med. Sci., Jan., 1902.

[304] Wolownik-Charkow: Virchow's Archiv, Bd. clxxx, S. 225, 1905.

[305] Müller: Münch. med. Woch., Bd. li, S. 199 u. 262, 1904.

[306] Braun: Berl. Klinik, Bd. xvii, Nu. 1, S. 16, 1904.

[307] Neugebauer: Centralbl. f. Chir., Bd. xxx, Nu. 5, S. 1417, 1903.

[308] Taramasio: Rev. Méd. de la Suisse Rom., Aug. 20, 1902.

[309] F. E. Hopkins: New York Med. Jour., Aug. 25, 1900.

[310] Kyle: Therap. Gaz., July 15, 1902.

[311] Seitz: Jour. of Ophthal., Otol. and Laryn., Mar., 1901.

[312] S. Solis-Cohen: *Ibid.*, May, 1902.

[313] Bloch: Medical Record, July 6, 1901.

In large therapeutic doses given hypodermically or endovenously, the adrenal extractives increase markedly the force of the cardiac contractions. This is the result of two consecutive effects of the drug: the *first* of these is the direct action: as normally the secretion of the adrenals stimulates the right ventricle while passing through it on its way to the lungs with the blood of the inferior vena cava,* the presence of an excess of adrenal principle in this blood increases this action on cardiac dynamism.* This occurs only when the adrenal extractive is not converted into adrenoxidase before reaching the heart.* The *second* action is indirect, but that which prevails in every instance.* The addition of adrenal extractive to the adrenoxidase—oxyhæmoglobin—already in the blood, increases its catalytic and oxygenizing power, and the functional activity of the heart is increased as well as that of all other organs.*

The passage of the adrenal secretion into the inferior vena cava and its action on the heart having been studied in detail in the thirteenth chapter, only a few of the main facts will be rehearsed here. Brown-Séquard, in 1853, found that the blood of the vena cava contributed to the heart's contraction. Oliver and Schäfer,[224] referring to the use of a solution of adrenal extract in saline solution, write: "We have in this way administered large doses of the extract to the dog, thereby producing the most violent cardio-vascular disturbance without causing a fatal result." The fact that extracts powerfully stimulate the heart was confirmed by Cybulski, Scymonowicz, Gottlieb and others. Vincent, Velich, Ott and others having obtained a similar effect after dividing the cord, while Cyon[225] found that it occurred notwithstanding division of the splanchnics, it is evident that the effect was not of central origin, it being well known, moreover, that it is not prevented by section of both vagi. That the action is local is further shown by the fact that Brown-Séquard found that removal of the adrenals greatly enfeebled the cardiac contractions, and that injections of adrenal extract restored them. Again, I (1903) showed that the dynamic agent in the venous blood of the vena cava (which Brown-Séquard thought was CO_2—a fact disproved) was the adrenal secretion. Seaman Douglass (1905) found that an adrenal solution caused a detached heart immersed in it at once to resume beating. The oxidizing activity of the blood on the adrenal secretion is given below.

That a therapeutic dose influences the heart by increasing the activity of its cellular exchanges, as it does that of all other tissues rather than by a direct action, is self-evident. Langlois,[226] and Carnot and Josserand[227] found experimentally that the adrenal active principle disappeared on entering the blood, while Embden and von Furth[228] found that it was oxidized in the latter, though not *in vitro*.

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* *Author's conclusion.*

[224] Oliver and Schäfer: Jour. of Physiol., vol. xvii, p. 9, 1894-95.

[225] Cyon: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 541, 1906.

[226] Langlois: Archives de physiol., T. x, p. 124, 1898.

[227] Carnot and Josserand: C. r. de la Soc. de biol., p. 1472, 1902.

[228] Embden and von Furth: Hofmeister's "Beiträge z. chem. Physiol. u. Path.," Bd. iv, S. 421, 1903.

The muscular elements of the vessels being also the seat of excessive metabolism,* another prominent symptom shows itself: viz., elevation of the blood-pressure. This in turn gives rise to a third phenomenon: slowing of the pulse owing to the greater resistance offered by the blood-column to the cardiac muscle.*

That hypermetabolism in the muscular layers of vessels causes vasoconstriction has already been sustained in the foregoing pages by considerable evidence. It is shown, moreover, by the fact that adrenal extractives, when administered during a prolonged period, produce arteriosclerosis, as recently shown by Josué,[229] Erb,[230] von Rzentkowski[231] and others. Oliver and Schäfer[232] showed twelve years ago that adrenal extract caused contraction of the blood-vessels by acting directly on their walls. In the light of the foregoing data, this is readily accounted for by the fact that it enhances excessively intracellular metabolism in the vascular elements, the vessels being thus caused to contract violently. The smaller the caliber of a vessel, therefore, the greater the chance of its lumen being obliterated. Now, the vasa vasorum have long been known to take a prominent part in the pathogenesis of arteriosclerosis. Cowan[233] states, in fact, that the "vasal changes may, in some cases, be the only visible lesion," and refers to cases in which he says "the interference with the vascular supply from the vasal vessels produced medial and intimal necrosis." Councilman's[234] study of 41 autopsies showed that in the nodular form the primary alteration consisted "in a degeneration or a local infiltration in the media and adventitia, chiefly about the vasa vasorum." The manner in which injections of adrenal extract can give rise to the arterial lesions is now plain. By closing the vasa vasorum, they arrest the nutrition of the vascular walls, and the lesions of arteriosclerosis follow. That lesions of the vasa vasorum are actually present was recently confirmed by Scheidemantel,[235] Marini[236] and Papadia.[237]

Poisoning.—In toxic doses, adrenal extractives, by causing excessive metabolism in the muscular elements of all vessels—excepting the capillaries, which are not provided with a muscular coat*—provoke so intense a general vasoconstriction in animals that all the organs are dangerously engorged. When death occurs its direct cause is pulmonary congestion and œdema and the consequent asphyxia.

There is at first more or less irritability, excitement and restlessness, soon followed by stiffness of the muscles, with perhaps spasmodic movements, or tremors. Gradually as the blood-pressure rises all capillaries become so gorged with blood that hæmorrhage from the nose and mouth, hæmaturia, bloody diarrhœa, cutaneous œdema and ecchymosis may occur; the caliber of the arterioles is soon sufficiently reduced, however, to impede circulation* and the symptoms of cutaneous ischæmia appear, viz., marked hypothermia, and anæsthesia. This is accompanied by great prostration, paralysis (beginning in the lower limbs), labored respiration, at first rapid, then slow and shallow, feeble heart action and finally death from asphyxia. This is preceded in some instances by convulsions, due to the accumulation of toxic wastes.

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* *Author's conclusion.*

[229] Josué: C. r. de la Soc. de biol., vol. lv, p. 1374, 1903.

[230] Erb: Wiener med. Presse, Bd. xlv, S. 854, 1904.

[231] von Rzentkowski: Berl. klin. Woch., Bd. xli, S. 830, 1904.

[232] Oliver and Schäfer: Jour. of Physiol., vol. xvi, p. 1, 1894.

[233] Cowan: Practitioner, Mar., 1906.

[234] Councilman: Osler's "Practice of Medicine," third edition, p. 771, 1898.

[235] Scheidemantel: Virchow's Archiv, Bd. clxxxi, S. 426, 1905.

[236] Marini: Gazetta d. Ospedali, Feb. 19, 1905.

[237] Papadia: Riv. di patol. nerv. e mentale, Mar., 1906.

In man, besides the untoward effects produced by the local action of adrenal extractives, referred to on page 1171, any of the morbid effects observed in animals may appear after injections into the tissues or circulation. The usual symptom-complex due to an excessive, though not necessarily fatal, dose is: preliminary restlessness, then weakness and staggering. Gradually as the general vascular pressure increases, the blood-column crowds the heart* and may give rise to marked cardiac pain, the pulse being hard and tense. This is attended by free passive perspiration, also of vasoconstrictor origin.* Gastric, bronchial and other capillaries may be ruptured by the pressure of blood into them,* and hæmatemesis, hæmaturia, etc., may occur. When the arterioles are sufficiently contracted to interfere with the circulation* the extremities and even the body may become very cold. Death may then occur by cardiac arrest from three factors: 1st, owing to the pressure upon it of the blood-column;* 2d, excessive constriction of its arteries, including the coronaries, which, contrary to prevailing teachings, are also supplied with vasomotor nerves;* 3d, arrest of the respiration by vasoconstrictor interference with the progress of the blood to the pulmonary alveoli.*

Swale Vincent[illegible] states that "the first effect noticeable in dogs is excitement. There is increased muscular activity which passes into a stage of agitation with tremors." The hæmaturia and the bleeding from the mouth and nostrils observed in various animals by the same investigator[illegible] is, he writes, "probably the expression of the high blood-pressure, brought about by the extract." These phenomena are evidently not of central origin, since he also found that destruction of the spinal cord in frogs did not prevent them. Pellacani,[230] who was the first to study the toxicology of adrenal extract in animals, found that such effects were only produced by very large doses, a fact subsequently confirmed by Swale Vincent.[231]

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* *Author's conclusion.*

[illegible] Swale Vincent: Jour. of Physiol., vol. xxii, p. 270, 1898.

[illegible] Swale Vincent: *Ibid.*, vol. xxii, p. 111, 1897.

Pellacani observed congestion of the liver, spleen and kidneys, and other structures, and when death was delayed, atrophy of these organs —a fact which indicates subsequent constriction of the arterioles and the resulting arrest of nutrition. The engorgement of all organs was also witnessed by Taramasio,[232] Cybulski,[233] and others.

Hultgren and Andersson[234] found that sufficient quantities of the extract caused death in the rabbit by provoking pulmonary œdema and sometimes hæmorrhage. These authors and Cybulski ascribe death caused by adrenal extracts to this condition. Gourfein[235] attributed it to asphyxia. Abel[236] and Abbott[237] both observed that epinephrin caused death by arresting the respiration. Indeed, Swale Vincent[238] found that the blood of one of his animals (dog) had become venous throughout the body. This illustrates the extent to which the œdematous lungs prevent aëration of the blood. On the other hand, Cybulski showed that artificial respiration kept the experimental animal alive, normal breathing being subsequently restored.

Therapeutics.—As the uses of adrenal gland have been treated at length in the first volume (pages 748 to 762 inclusive), its main indications will only be mentioned here. Adrenal gland is used in disorders due to a gouty "diathesis," as *hay-fever,* and *asthma*—a result accounted for by its power to enhance metabolism and therefore catabolism of toxic wastes. In asthma due to low vascular tension, suprarenalin or epinephrin, 10 minims of the 1:1000 solution in 1 dram of saline solution intramuscularly, promptly arrests a paroxysm, by supplying the blood with more adrenoxidase, *i.e.,* with oxygen.*

The manifest influence adrenal gland has on nutrition also accounts for its beneficial action in adynamic disorders,* *neurasthenia* and *surgical shock,* for example. This applies also to *cardiac disorders* characterized by weakened systole or dilatation and their complications.

Adrenal gland has been found of value in neurasthenia by many observers, including Huchard, and, as already stated, in shock, saline solution (1 in 50,000) being used as excipient. In cardiac disorders it has been recommended by several clinicians, including Mankowsky,[239] Floersheim,[240] and Deeks.[241] Mankowsky specifies that the most useful application of adrenal gland is in cardiac weakness and threatening collapse. Floersheim found it effective where our usual remedies had failed. Deeks obtained not only marked improvement in cardiac weakness, but disappearance of attending œdema. Boy-Teissier[342] obtained excellent results in cases of weak heart with general cyanosis and great cardiac dilatation.

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* *Author's conclusion.*

[230] Pellacani: Arch. per le Scienze med., vol. iii, p. 24, 1879.

[231] Swale Vincent: Jour. of Physiol., vol. xxi, p. 25, 1897.

[232] Taramasio: *Loc. cit.*

[233] Cybulski: Wiener med. Woch., Bd. xlvi, S. 214, 255, 1896.

[234] Hultgren and Andersson: Skandin. Arch. f. Physiol., Bd. ix, p. 73, 1899.

[235] Gourfein: Revue méd. de la Suisse Rom., vol. xv, p. 613, 1895.

[236] Abel: Zeit. f. physiol. Chemie, Bd. xxviii, S. 318, 1899.

[237] Abbott: Jour. of Med. Research, vol. iv, p. 329, 1903.

[238] Swale Vincent: Jour. of Physiol., vol. xxii, p. 270, 1898.

[239] Mankowsky: Russian Arch. of Path., Clin. Med. and Bact., Mar., 1904.

[240] Floersheim: New York Med. Jour., Oct. 6, 1900.

[241] Deeks: Montreal Med. Jour., Nov., 1901.

Addison's disease, whether due to organic lesions of the adrenals themselves or of the nerves or ganglia through which they receive their impulses, is attended by lowered metabolism, hypothermia, and low blood-pressure. Adrenal gland is indicated *in doses sufficient to raise both the latter and the temperature to normal and keep them so,* i.e., 3 grains during meals.

In this disease, the vitality is so reduced that, as stated by Rolleston,[343] the cases sometimes emit a cadaveric odor. Some clinicians, including Senator,[344] have noted no modification of the nitrogen output; some found that it was increased; others that it was decreased. In literature, these results are recorded as discordant; but this is not warranted in the light of my views. They merely indicate that metabolism is more impaired in some cases than in others, owing to greater destruction of the adrenals or of their nerves, and that where no perceptible effect is obtained from adrenal extractives, it is because the supply is not adequate, both as to quality and quantity, to restore the vital equilibrium—to compensate, in other words, for the loss of those organs which sustain the vital process by supplying the tissues with oxygen. In an analysis of 97 cases reported in literature, by E. W. Adams,[345] in which adrenal preparations were used, 7 cases were made worse; 43 derived no real benefit; 31 showed marked improvement, and 16 were "permanently relieved." The pigmentation waned in most of the cases improved. This affords a marked contrast with Lewin's 800 reported cases treated by other methods,[346] of which 28 cases were improved and 5 cured. (Addison's disease is treated in full in Chapter II.)

In hæmorrhagic disorders, the identity of adrenoxidase as the fibrin or coagulating ferment,* renders adrenal extractives effective as hæmostatics, whether applied externally or given internally. Hence its recognized value in *epistaxis, hæmoptysis, hæmatemesis, intestinal hæmorrhage,* the dose of adrenalin chloride when given orally varying from 5 to 30 drops every three hours, according to the urgency of the case. Even the hæmorrhages of *hæmophilia* can be promptly arrested by the local application of adrenal extractives. The internal use of thyroid gland, which actively stimulates the adrenal center and causes a marked increase of adrenoxidase,* masters the primary disorder itself. (See also Adrenal Opotherapy, vol. i, p. 750.)

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* *Author's conclusion.*

[342] Boy-Teissier: Arch. gén. de méd., Aug. 23, 1904.

[343] Rolleston: Allbutt's "Practice of Medicine," vol. v, p. 540, 1897.

[344] Senator: Charité-Annalen, Jahrg. xxii, S. 226, 1897.

[345] E. W. Adams: Practitioner, Oct. 1902.

[346] Lewin: Allbutt's "Practice of Medicine," vol. v, p. 561, 1897.

ANTITOXINS.

Source and Chemical Nature.—None of the prevailing theories of immunity explain the origin or mode of action of antitoxin. This is due to the fact that Ehrlich's side-chain theory—though extremely elucidative in many directions—has diverted the attention of pathologists from the true source of the constituents of this substance: the adrenals and other ductless glands.*

As to the origin of antitoxin, Ritchie in an impartial review as president of the section of Pathology of the British Medical Association,[347] said recently: "We must admit that at present we know of no definite facts which point to the place of origin of antitoxin;" and, moreover, referring to Ehrlich's theory: "The view that the saturation of the side-chains of the cell [the tissue-cell] with toxin made them drop off with their burden of toxin always appeared to me to be hardly tenable, in view of the fact originally put forward by Ehrlich that the reason for the affinity of toxin for the cell was probably to be found in the fact that the toxin closely resembled the normal food of the cell. It would be of little use to the cell if a side-chain should straightway drop off into the serum whenever a food particle became attached to it. *The whole view was too theoretical.*"

The practical side of the question is aptly described by H. C. Wood, Sr. and Jr., in a recent edition of their text-book:[348] "The mode of action of the antitoxin in infectious diseases has been the subject of a large amount of surmise and study, but while a number of interesting theories have been suggested, notably that of Ehrlich, it must be confessed that we have no positive knowledge of the manner in which this substance acts in infectious diseases."

Again, as stated by H. Gideon Wells,[349] according to the side-chain theory, "the antitoxin consists of cell receptors that have been produced in excess and secreted *by the cells into the blood*," referring to the *tissue*-cells. Ehrlich has failed to demonstrate this fact. On the other hand, considerable evidence is available, we have seen, to show that it is through the intermediary of the leucocytes that the bacteriolytic and antitoxic substances reach the blood. Ainley Walker,[350] for instance, writes: "A definite relation exists between the mass of the leucocytes added [to serum] and the degree of bactericidal power obtained (Bordet). Again, a bacteriolytic pleural exudate has been made *entirely inactive* by the removal of its leucocytes, active again on their replacement (Denys and Havet)." From this and other facts submitted, the author concludes that "the addimentary ferment is definitely associated with the leucocytes, and is not a ferment circulating freely in the blood-plasma as Ehrlich teaches."

Before Ehrlich introduced his side-chain theory, and ever since, numerous investigators have urged the importance of the ductless glands and internal secretions as important factors in the destruction of poisons. "Some years ago," writes Charrin,[351] "the physiology of the adrenals was singularly obscure. The foresight of Brown-Séquard, the interesting researches of Langlois, Abelous, and those of Albanese, Zucco, etc., akin to our own, have brought these structures within the group of organs endowed with antitoxic functions. With Langlois, I ascertained that a given quantity of these organs weakened the action of certain alkaloids, especially nicotine." Other organs are referred to in the same sense. "As to the antitoxic functions," writes Charrin, "one may depend upon a series of viscera, first of all, the liver, the pituitary body, the adrenals, the pancreas, the kidneys, the spleen, etc."

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* *Author's conclusion.*

[347] Ritchie: Brit. Med. Jour., Sept. 10, 1904.

[348] H. C. Wood, Sr. and Jr.: "Therapeutics," thirteenth edition, p. 544, 1906.

[349] H. Gideon Wells: "Chemical Pathology," p. 128, 1907.

[350] Ainley Walker: Lancet, Oct. 19, 1901.

[351] Charrin: Semaine médical, vol. xv, p. 147, 1895.

The most recent writers speak in the same trend. While Ritchie, alluding to the side-chain theory in the address previously referred to, concludes that "we must keep an open mind for admitting that the cells pathogenically affected by a toxin may not be the cells of origin of antitoxin," Gruber and von Pirquet[552] urge that the formation of antibodies, contrary to Ehrlich's view, occurs in an entirely different place than the action of the toxins, and that they had the character of internal secretions. Sir A. E. Wright[553] also emphasized this kinship, though asserting that "their origin in the body was unknown," by the statement, "all the protective substances which were involved in the cure of disease were to be regarded as produced by internal secretions," urging that "if the laws by which such substances were produced were known," we could "call forth" their production.

This is not intended to imply that the side-chain theory has contributed nothing to our knowledge; Ehrlich's own labors in this connection and those of the many investigators who have taken up his views have done much to elucidate the relations between the various bodies which take part in the immunizing process. Moreover, Ehrlich has himself forever set aside the erroneous view that antitoxin is nothing but transformed toxin, and placed on a solid foundation the fact that the protective bodies were products of cellular activity. What I claim is that the cells in general are not, as Ehrlich believes, the source of antitoxin, and that the substances of which it is composed are the products of the organs referred to below.

Antitoxin is blood-plasma containing adrenoxidase, nucleoproteid and digestive triads (trypsin, etc.), and thyroiodase. It is produced in animals under the effects of injections of various toxins, as a result of the stimulating action of the latter upon the test-organ, and through it upon the adreno-thyroid center. The resulting excess of adrenoxidase excites, in turn, an overproduction of pancreatic ferments and leucocytes, by increasing metabolic activity in the pancreas and leucocytogenic tissues. The thyroiodase is due to direct excitation of the thyroid. Antitoxin is the homologue of auto-antitoxin formed in the blood under the influence of mercury, iodine, and other drugs.*

Although, as stated by Gideon Wells,[554] the chemical nature of antitoxins "is as entirely unknown as is the nature of the toxins," the few facts available point to the presence of all the constituents which compose what, in the preceding articles, I have referred to as "auto-antitoxin."

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* *Author's conclusion.*

[552] Gruber and von Pirquet: Münch. med. Woch., Bd. 1, S. 1259, 1903.

[553] A. E. Wright: Brit. Med. Jour., Mar. 19, 1904.

[554] Gideon Wells: *Loc. cit.*, p. 139.

That antitoxin is blood-plasma unusually rich in its normal immunizing constituents is suggested by various facts. A careful chemical study led Viquerat[illegible] to the conclusion that, barring the presence of lactates in antitoxin and other sera, the latter differed in no way qualitatively from normal serum. F. Warren White[illegible] studied the germicidal action of serum taken from healthy persons; from patients suffering from various diseases and from the body just before and after death. All showed marked bacteriolytic properties on the typhoid bacillus. This was completely destroyed, however, by heating the serum to 55° C. Thus, the blood-serum during health and disease is qualitatively similar to antitoxin. In fact, as stated by B. Meade Bolton,[illegible] horses used for the production of diphtheria antitoxin, often "possess antitoxin normally in their blood."

As to *adrenoxidase,* the principle increased is, of course, the adrenal secretion, to which Auld and others refer as "a colloid." Gideon Wells,[illegible] alluding to antitoxins, remarks: "In any event they behave as colloids"—a fact which suggests that in keeping with the evidence previously submitted, the plasma and red corpuscles are correspondingly richer in oxyhæmoglobin. Again, we have seen that adrenoxidase is a globulin. William H. Park, of the New York Health Department,[illegible] refers to the fact that "recent investigations have connected antitoxins and *globulins* so closely" that "we may consider it a probability that the antitoxins are globulins or globulin-like substances:" he was led experimentally to confirm this fact. I have pointed out, furthermore, that the adrenal principle is the general catalytic of the organism and the "ferment of ferments." Now, Ehrlich has shown that a given quantity of antitoxin will not only neutralize a fixed quantity, say 100 lethal doses of toxin, but that it will keep on neutralizing until very large quantities are rendered harmless. Bashford[illegible] also observed that "the poisonous action of the lethal dose of toxin may be abolished within the time limit by the addition of a very small quantity of antitoxin." This, of course, is due to the presence of a ferment—trypsin, perhaps; but this in itself proves the presence of the adrenal active principle, since it is to this principle that every trypsin owes its activity as such, while we have seen that, as stated by Moore,[illegible] "ferment actions" are "catalytic reactions."

Finally, it becomes a question whether toxins (by stimulating the test-organ and through it the adreno-thyroid center) can provoke an increase of this globulin, as they do of adrenoxidase. This is well shown in the following lines by W. H. Park:[illegible] "Horse numbered 137 when first obtained contained 3.2 per cent. globulin and 3 units of antitoxin in each c.c. It is of some interest to note that this is the largest amount of normal antitoxin ever noted by us in an *untreated* horse. Three months later, after repeated *injections of toxin,* the *globulin,* as tested by Mr. Atkinson, was 8.2 per cent., and the antitoxin 1200 units per c.c. Three weeks later toxin injections having been *omitted,* the globulin was 5.9 per cent. and the antitoxin 650 units per c.c. Still ten days later the globulin was 4.7 and the antitoxin 400 units." The importance of adrenoxidase in the process now asserts itself. "As investigations progressed," writes Park,[illegible] "it has become more and more evident that the antitoxic substances in the blood are closely combined

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[illegible] Viquerat: Centralbl. f. Bakt., Parasit. u. Infekt., Bd. xxi, S. 581, 1[illegible].

[illegible] F. Warren White: Boston Med. and Surg. Jour., Feb. 23, 1[illegible].

[illegible] B. Meade Bolton: Jour. of Exper. Med., July, 1[illegible].

[illegible] Gideon Wells: *Loc. cit.,* p. 140.

[illegible] W. H. Park: Archives of Pediatrics, Nov., 1[illegible].

[illegible] Bashford: Lancet, Oct. 17, 1903.

[illegible] Moore: Schäfer's "T. B. of Physiol.," vol. i, p. 317, 1[illegible].

[illegible] W. H. Park: *Loc. cit.*

[illegible] Park: Pediatrics, Aug. 15, 1[illegible].

with the globulins of the blood, and that whatever precipitates them precipitates the antitoxin also. In fact, without globulin there appears to be no antitoxin, and wherever antitoxin exists, globulin does also."

Antitoxin contains *nucleo-proteid* besides nuclein. As to nuclein, Szontagh and Wellmann[334] found that it was present in antitoxin as well as in horse-serum, as nucleo-albumin. E. W. Walker[335] noted that "the bacteriolytic power of a fresh serum [antitoxin] rapidly diminishes both in the immune and normal sera, and ceases to be recognized within a few days from the time of bleeding." I have shown that this is due to the presence of the phosphorus-laden nuclein, *i.e.*, the body (Pflüger's "reducing substance") which promptly takes up the oxygen in shed blood. As to proteids, Wells[336] concludes, that "taken altogether, the evidence indicates a closer resemblance of antitoxins to proteids than has been shown for the toxins, and all attempts to separate antitoxins from proteids have so far failed." As shown below (Park and Throne) these bodies, nuclein and proteid, can be isolated from antitoxin as nucleo-proteid.

The various *hydrolytic triads*, including trypsin, secreted in the plasma by leucocytes, represent, from my standpoint, we have seen, Ehrlich's "complement" or "addiment," which Ehrlich and Morgenroth[337] define as "the unstable (labile) *ferment-like* body which effects the solution of the blood-cells," *i.e.*, hæmolysis. These investigators state that a serum described by Bordet and their own, derived from goats, "lost its hæmolytic power when heated for half an hour to 56° C." This they state has been shown by Buchner to be true of all normal hæmolytic sera. Whether the temperature be 56° or 55° is evidently immaterial, for Wassermann, alluding to Ehrlich and Morgenroth, says that they made hæmolytic serum "inactive by heating to 55° C., so that," he adds, "it contained only the substance sensibilisatrice." Having shown[338] that this latter substance is adrenoxidase plus thyroidase, it is evident that the trypsin alone was destroyed. Now, since as shown above, blood-serum and antitoxin are similar qualitatively, if antitoxin also contains the ferment, it should likewise be destroyed at this temperature. Wells[339] writes, "If we heat bactericidal serum made by immunizing an animal against bacteria, say the cholera vibrio, at 55° for fifteen minutes, it will be found to have destroyed the power of destroying these organisms." We have seen, moreover, under "adrenoxidase" that antitoxin, as noted by Ehrlich and Bashford, acts as a ferment. The formation of thyroiodase (opsonin) was described in the preceding chapter.

Although the various germicidal and antitoxic constituents of the blood are included in antitoxin, they are not all required to produce its beneficial effects. The latter are due to the large proportion of adrenoxidase that antitoxin contains.[*]

It was in the course of experiments to prevent the untoward effects sometimes produced by injections of antitoxin: eruptions, hæmolysis, etc., that William H. Park, of New York, observed the fact, mentioned above, that "without globulin there appears to be no antitoxin," and "that wherever antitoxin exists globulin does also." Inasmuch as adrenoxidase is the only globulin among the constituents of antitoxin, it follows that it is to adrenoxidase that we must ascribe the curative action of antitoxin. That such is the case is shown in another way. We have seen that the power of normal serum to destroy the red corpuscles of another animal (hæmolysis), *i.e.*, its digestive power, and also that of bactericidal serum derived from an immunized animal—and, therefore, antitoxin—were destroyed when these sera were heated from fifteen to thirty minutes at 55° C. An important feature of these experiments, however, is that they were conducted *in vitro*, and that as far as the antitoxin is concerned, heating to 55° C. does not destroy its germicidal and antitoxin effect when injected into the living body. This was shown in the course of experiments by Atkinson.[570] He found that when a solution of globulin (precipitated from antitoxic serum as well as ordinary serum by magnesium sulphate) was saturated with sodium chloride and then gradually heated to 72° C., precipitates were formed which, in the *various antitoxins, remained antitoxic.* Now, as 55° C. destroys the digestive triads (complement), and even thyroidase (opsonin), which is destroyed at from 60° to 65° C., there was nothing left in the precipitate as active agent but adrenoxidase, which, we have seen, resists all temperatures up to 100° C., and even that several hours.

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[*] *Author's conclusion.*

[334] Szontagh and Wellmann: Deut. med. Woch., Bd. xxiv, S. 421, 1898.

[335] E. W. Walker: Lancet, Jan. 4, 1902.

[336] Wells: *Loc. cit.*, p. 141.

[337] Ehrlich and Morgenroth: "Collective Studies of Immunity," Bolduan's Transl., p. 11, 1906.

[338] *Cf.* preceding chapter.

[339] Wells: *Loc. cit.*, p. 144.

Physiological Action.—The various antitoxins, when administered subcutaneously during health or disease, increase the bacteriolytic and antitoxic properties of the blood by augmenting, in proportion with the quantity administered, its content in auto-antitoxin, the homologue of all antitoxins.* As is the case when thyroid extract or adrenal extractives, adrenalin, epinephrin, etc., are used, metabolism is increased,* sufficiently so in some instances, to produce fever, leucocytosis, rheumatic pains due to accumulation of wastes, and even renal disorders.

There is ample evidence to the effect that antitoxin injections increase metabolism, while the febrile phenomena point directly to the presence of an excess of adrenoxidase in the blood. A few illustrations will emphasize these facts.

Coldefy,[571] for example, out of 400 cases in which antidiphtheritic serum was injected as a prophylactic measure, observed six in which there was pyrexia, which appeared and disappeared rapidly. In eight, the pyrexia lasted a short time, while in a tuberculous patient it was very marked, and lasted several days. Rolleston[572] states that muscular and joint pains occurred in 10.24 per cent. and pyrexia in 15.01 per cent. of 600 cases treated in the Metropolitan Asylums. He states, moreover—thus unconsciously contributing testimony to the curative value of the enhanced metabolism—that in the 600 cases treated in the Metropolitan Asylums upon which his conclusions are based, that as a general rule, the more marked the antitoxin reaction, the better the prognosis. Mongour[573] found that the excretion of nitrogen wastes was increased, and also that the chances of recovery were greater when the urea output was marked.

J. Ewing[574] observed that antitoxin caused an increase of multinuclear leucocytes within thirty minutes. In severe cases hyperleucocytosis and fever occur. Kucharzewski[575] also found that moderate doses of diphtheria, tetanus, or antistreptococcus serum produced a leucocytosis lasting several days.

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* *Author's conclusion.*

[570] Atkinson: Jour. of Exper. Med., vol. v, p. 67, 1900.

[571] Coldefy: Birmingham Med. Review, Feb., 1905.

[572] Rolleston: Practitioner, May, 1905.

[573] Mongour: Jour. de méd. de Bordeaux, vol. xxv, p. 217, 1895.

[574] J. Ewing: New York Med. Jour., Aug. 10, 17, 1895.

The albuminuria, following the use of antitoxin, is sometimes ascribed to the disease, but Adae,[576] having examined the urine in 25 cases before using antitoxin, found albuminuria in only one instance, while in all it appeared at once after the injection. This symptom was observed to follow injections of antitoxin in 42.5 per cent. of the cases by Bokai,[577] in 64 per cent. by Fürth,[578] and 72 per cent. by Soltmann,[579] and 64.8 per cent. by Schröder.[580] In animals Vissmann[581] ascertained that doses in the relative strength given to children caused nephritis.

Untoward Effects.—The morbid phenomena that follow large therapeutic doses of diphtheria antitoxin are as follows: fever, due to increased metabolic activity,* attended, if metabolism becomes excessive,* with diminution of the red corpuscles, sometimes to 3,000,000, and albuminuria. When metabolism is excessive, it causes, owing to involvement of the vascular walls, correspondingly marked vasoconstriction* and the arterioles of the pituitary body and heart, among others, being almost closed, the functions of these organs are inhibited,* giving rise to faintness, coldness with feeble and irregular cardiac action. In rare cases, death occurs. When constriction of the peripheral arterioles persists there occurs, after a few days, accumulation of waste products of various kinds* in the cutaneous tissues, and eruptions, especially urticaria and erythema, may appear, along with increased nitrogen and phosphoric acid secretion and albumin. This may last several days and be attended with œdema, bloody diarrhœa, acute joint pains, myalgias and neuralgia due to intense congestion of the various structures involved.* The inordinate consumption of chromatic elements in the nervous elements attending this excessive metabolism,* may give rise to paresis or paralysis of muscles in different regions, especially those of the palate.

These morbid symptoms are familiar to all practitioners. They obviously correspond with those of the agents previously reviewed and indicate further the similarity of their action. The capillary engorgement also affects the internal organs. Thus Kossorotoff[582] found that in rabbits, injections of antitoxin caused a marked hyperæmia of the liver, kidneys and spleen, and marked leucocytosis. As instance of excessive constriction of the arterioles I may mention a case reported by J. P. Marsh,[illegible] in which 1500 units caused in 10 minutes intense dyspnœa, cyanosis and a comatose state, during which the patient, a woman of 30 years, was practically blind and complained of general numbness. This was followed by severe itching and "stinging rash," due here to secondary overdilation of the arterioles and hyperæmia of the skin and its sensory nerve endings. The vasoconstrictor action may occur immediately. Thus E. R. Houghton[illegible] observed an instance in a pregnant woman, to whom another practitioner administered a protective injection. "At once she felt faint and very cold, but after a few moments rallied and went home." Her 8-months fœtus, which had shown vigorous movements until then, no longer gave evidence of life and was macerated when born two weeks later. Rolleston[illegible] states that the eruptions, the principal varieties of which are: the scarlatiniform, the urticarial and the circinate erythematous, depend directly upon the size of the dose.

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* *Author's conclusion.*

[575] Kucharzewski: Arch. intern. de pharmacod. et de thérap., T. xii, p. 117, 1903.

[576] Adae: Med. Correspondenzblatt des wurttemb. Aerzt. Landesv., Nu. 12, 1895.

[577] Bokai: Deut. med. Woch., Bd. xxi, S. 222, 1895.

[578] Fürth: Münch. med. Woch., Bd. xlii, S. 689, 1895.

[579] Soltmann: "Ueber die Erfolge mit Diphtherie Heilserum," 1896.

[580] Schröder: Münch. med. Woch., Bd. xliii, S. 327, 351, 1896.

[581] Vissmann: Med. Record, Sept. 14, 1895.

[582] Kossorotoff: Praktitcheskoi Medicini, Dec., 1895.

When an antitoxin divested by heat or other physico-chemical procedures of its trypsin (complement) is employed, the digestive activity of the blood's auto-antitoxin is not reduced, since it is adrenoxidase (the specific immune body) which endows all ferments with their power as such.* The proferment fibrinogen is in reality alone destroyed in the antitoxin;* and, as it confers on the ferment merely its specific character (proteolysis), its absence does not affect the result, as considerable trypsin, and therefore trypsinogen, is available in the blood.* This proves, however, that *adrenoxidase is the active agent in all antitoxins.**

R. B. Gibson,[illegible] in reference to the antitoxin submitted to temperatures which destroyed their ferment or complement, states that "Park studied the possibility of eliminating serum rashes by treating a considerable number of cases with an antitoxic globulin prepared by Atkinson. Rashes were still produced." Recently Park and Throne[illegible] reported a series of cases in which antitoxin from "the *nucleo-proteids* and insoluble globulins present in the Atkinson preparation were eliminated." They obtained somewhat better results (due probably to the loss of 30 per cent. of units during the process), but found that "the antitoxic effect was identical with that of the whole serum." In fact, they "could not detect the slightest evidence that any desirable substance in the antitoxic serum is lost by the refining process." Thus, the elimination of nucleo-proteid does not affect the action of the globulin antitoxin any more than the destruction of the trypsin by heat. It is evident, therefore, that the active body in antitoxin is the only remaining one, adrenoxidase.

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* *Author's conclusion.*

[illegible] J. P. Marsh: Amer. Jour. Med. Sci., Dec., 1902.

[illegible] E. R. Houghton: Med. Record, Apr. 4, 1902.

[illegible] Rolleston: *Loc. cit.*

[illegible] R. B. Gibson: Jour. of Biol. Chem., vol. 1, p. 161, 1905-06.

[illegible] Park and Throne: Amer. Jour. Med. Sci., Nov., 1906.

Therapeutics.—All the disorders—*diphtheria, tetanus* and others—in which antitoxins are indicated being infectious, it is perhaps needless to state that the physiological action I describe in the foregoing pages accounts clearly for the beneficial effects obtained.

Another feature upon which some stress must be laid is that the physiological action of the antitoxins, as I interpret it, is identical with that provoked by the various drugs described in the present chapter—each of which likewise introduces its own array of evidence. *If*, therefore, *we grant life-saving properties to antitoxin*—which is undoubtedly the case in so far as diphtheria antitoxin is concerned—*we must concede the same value to drugs which are capable of evoking in the blood the formation of the same substance, i.e., auto-antitoxin.*

CHAPTER XIX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*).

THE SYMPATHETIC CONSTRICTORS AND THE CRANIAL STRICTO-DILATORS IN ORGANIC FUNCTION.

We have seen in the sixteenth chapter that the sympathetic system is autonomous as a functional entity, and that its governing center is located in the posterior pituitary, with the centers of motor nerves.

According to prevailing teachings, the sympathetic carries on several different functions. In a succinct review of the subject, W. S. Hall[1] states, for example, that the "more important functions" of the sympathetic system are the following: "(*a*) cardio*acceleration* and cardio*augmentation* through the branches from the cervical ganglia. (*b*) *Secretory* impulses to the salivary glands, the stomach, the pancreas, the liver, the small intestine, the large intestine, the kidneys. (*c*) *Vasomotor* impulses, *both constrictor and dilator*, to all arteries and arterioles. (*d*) *Motor* impulses to the *muscular coats* of the stomach and intestines, causing peristalsis and controlling the pylorus and the cardia of the stomach. (*e*) *Motor* impulses to the *muscularis mucosa* of the alimentary canal, causing movements of the mucosa."

Another function ascribed by physiologists to the sympathetic, is that of *inhibition*. In the heart, as is well known, this is believed to be the physiological function which counteracts cardiac acceleration; in the intestine it is thought by some to oppose peristalsis; it is also believed by many to inhibit the contraction of certain vessels, etc. As this inhibition is produced by stimulating the sympathetic nerves distributed to these various organs, we are brought to the conclusion, in view of the fact that a sympathetic nerve can awaken function by causing vasodilation, that it can also inhibit that function by causing vasocontriction, or, in other words, that a sympathetic nerve can inhibit its own functions.

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[1] Hall: *Loc. cit.*, p. 106, 1905.

That the whole scheme of sympathetic function, as now interpreted, is defective, appears to me very evident. Howell[3] rightly states that "few subjects in physiology are of more practical importance to the physician than that of vasomotor regulation; it plays such a large and constant part in the normal activity of the various organs." So great is this importance, in fact, that it is mainly because the whole question of vasomotor function has been obscured by the problematic rôles ascribed to it by physiologists, that the physiological action of drugs, and what Virchow has termed "physiologic pathology" have remained so obscure.

In the sixteenth chapter, I pointed out that the bulbar vasoconstrictor center was independent of sympathetic vasoconstrictor functions, and that it acted only as intermediary for the transmission of sympathetic impulses down the cord. The source of these impulses was shown to be the pituitary body, stimulation of which, as then shown, caused typical sympathetic vasoconstriction in the periphery and a marked general rise of the blood-pressure, owing to the resistance of the constricted arterioles to the general circulation. These and other facts led me to the conclusion that the neural or posterior lobe of the pituitary body was the seat of the *sympathetic center*. Returning to the confusing functions referred to above, it will now become evident that they are all experimental myths, and that the one function which the sympathetic fulfills—the only one fully sustained by experimental evidence—is that of a *vasoconstrictor of all the small arteries or arterioles.*

Inhibition, in the accepted sense, *i.e.*, a restraint of functional activity, has already imposed itself upon us in the preceding chapter, where we saw certain toxins and drugs cause excessive constriction of the vessels of the pituitary body and heart. That such vasoconstriction, whether produced by the latter or by too strong a current, must correspondingly reduce the caliber of a vessel and reduce the volume of blood passing through it is obvious. We have seen that, as shown by Brown-Séquard and Porter, the caliber of the coronaries can be

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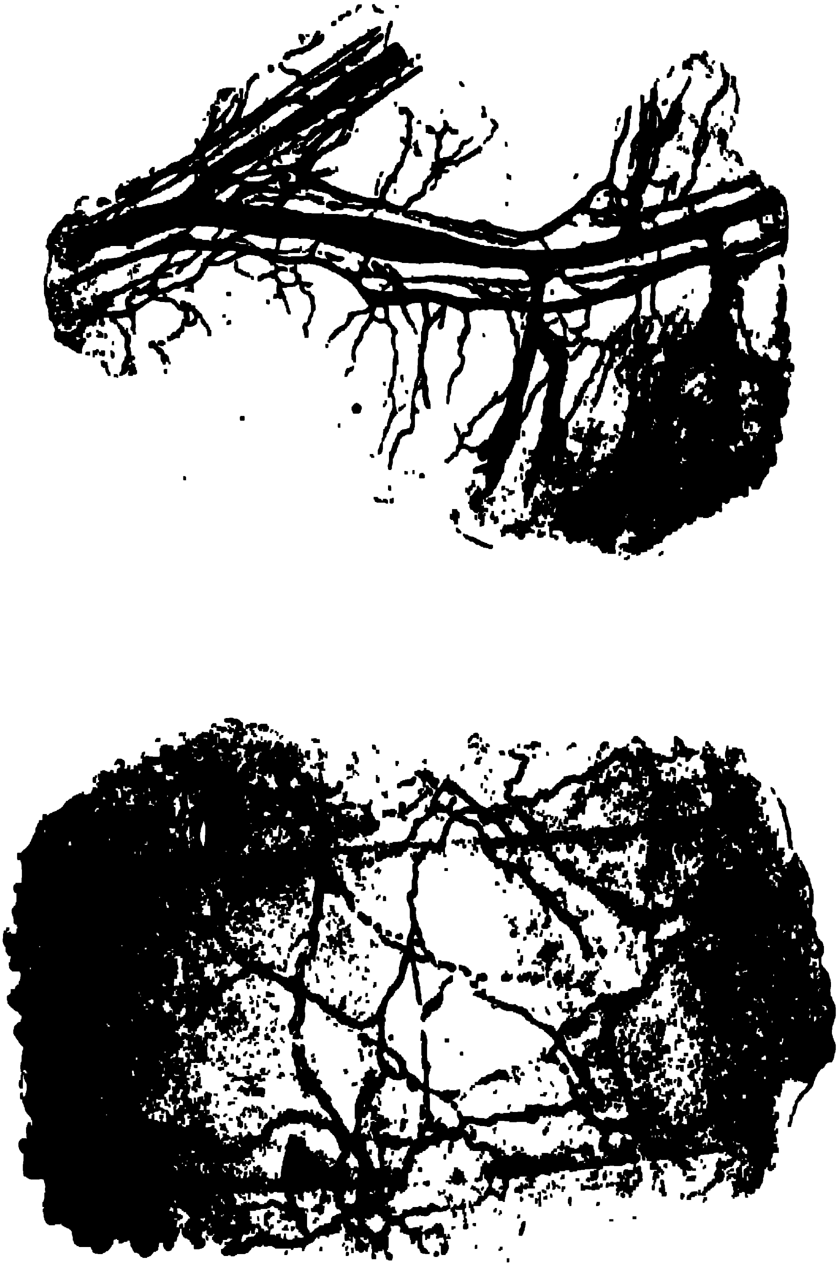
[3] Howell: *Loc. cit.*, p. 531, 1905.



VASOMOTOR NERVES OF THE CARDIAC CORONARIES. *[Heymans and Demoor.]*

actively reduced by stimulating the vagal vasomotor nerves, the origin of which I[3] traced to the vasomotor center. Physiological text-books, notwithstanding the evidence submitted by the above-named investigators and myself, still teach that the coronaries are deprived of vasomotor nerves; the plate reproduced herewith must convince them of their error, since it is a microphotograph of coronaries showing unmistakably the presence of these nerves, published over twelve years ago by Heymans and Demoor.[4]

The manner in which the heart is influenced plainly shows that inhibition is due merely to deficiency of blood in the myocardium. Hill[5] states that moderate stimulation of the vagus (which contains the vasomotor fibers) may reduce the output of blood from the heart 30 to 50 per cent. E. Weber[6] observed that during partial inhibition the cardiac contractions were weakened. Schiff[7] found that the muscular elements of the entire organ responded less or not at all to stimuli. François-Franck, Fischel[8] and others observed that the cardiac walls were softer than usual. Gaskell[9] characterizes as "most striking" the attending depression of activity.

Can we regard as a physiological or normal function a process which entails paralysis of the heart? In the preceding chapter we found that toxic doses of certain drugs could produce a similar effect—drugs which, in excessive doses, were capable of so violently stimulating the *vasomotor* center, that the caliber of the coronaries became sufficiently narrowed to reduce the quantity of blood in the cardiac muscle below the physiological limit, which means enough contractile power to project the blood into the lungs. That inhibition here is a process brought on *artificially* in the laboratory, or morbidly by a poison, seems plain.

This shows that excessive constriction of even large arteries (for the coronaries are large vessels, when compared to those supplied by sympathetic nerves) can arrest function.

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[3] Sajous: N. Y. Med. Jour., May 14 and 21, 1904.

[4] Heymans and Demoor: Mem. couron. de l'Acad. roy. de med. de Belgique, T. xiii, p. 1, 1894.

[5] Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 1, 1900.

[6] E. Weber: "Handw. d. Physiol.," Bd. ii, S. 42, 1846.

[7] Schiff: Archiv f. physiol. Heilk., 9 ter Jahrg., S. 22, 1850-51.

[8] Fischel: Archiv f. exp. Path. u. Pharm., Bd. xxxviii, S. 228, 1897.

[9] Gaskell: Schäfer's "T. B. of Physiol.," vol. ii, p. 169, 1900.

May we not expect that the "small arteries and arterioles of the body," in view of their diminutive caliber, will be constricted even more readily—sufficiently, in fact, to obliterate their lumen and arrest function?

That such is the case may be shown by the following evidence, which has been thought to prove the existence of "inhibitory" sympathetic fibers:—

"Section of the sympathetic paralyzes the *muscles of the vessels* which are located in the field of distribution of the great sympathetic," writes Morat,[10] "and its stimulation causes them to *contract*." This conclusion is based on another classical experiment by Claude Bernard, outlined by the same author, as follows: "Having cut the sympathetic in the neck of a rabbit, he observed that the temperature of the whole of the corresponding side of the head, especially of the ear, was remarkably raised. On making the counter-experiment by stimulating the superior end, he observed that the temperature fell below the original temperature, as Brown-Séquard had observed almost contemporaneously." The rise of temperature was, of course, due to the entrance of additional blood in the capillaries supplied by vessels innervated by the cut sympathetic, while conversely, stimulation of the upper end of the latter caused constriction of the same vessels, exsanguination of the same area and hypothermia. In other words, this illustrates the one function which the sympathetic carries on, but in the small vessels and arterioles *only*.

How "inhibition" can be provoked in these vessels will now appear. Morat[11] writes: "Dastre and Morat showed, in 1881, that stimulation of the great cervical sympathetic causes, in addition to the oculo-pupillary effects [described below], and of the constriction of the vessels of localities which are habitually obvious, like the ear, dilatation of those *of neighboring regions*, the upper and lower lip, the palatine arch, and this very clearly in the dog. Hence the sympathetic contains inhibitory vascular nerves." Interpreted from my standpoint, however, this does not indicate the presence of such nerves. Thus, Morat publishes the colored engraving reproduced below, in which the effects of stimulation of the sympathetic are clearly illustrated. Dilation of the pupil and exophthalmos are plainly shown, but the salient features are the *pallor* of one side of the tongue and ear, as contrasted with the *congestion* of the lips, gums and palatine arch of the corresponding side. Now, Morat ascribes the localized pallor to vasoconstriction—which is undoubtedly true; the congestion, however, he attributes to inhibition of this vascular constriction, the sympathetic being supposed to send vasodilator fibers to the vessels of the corresponding area. The nerve is thus regarded as acting simultaneously as constrictor and dilator, though in different areas. From my standpoint, a simpler and more logical explanation asserts itself, *viz.*, the *arterioles* of the pale area being *alone* supplied by the cervical sympathetic, they contract when the latter is stimulated; these small vessels being markedly constricted as shown by the pallor, the circulation through them is blocked and the blood accumulates in the other vessels—those of the congested area. That the vessels of one side

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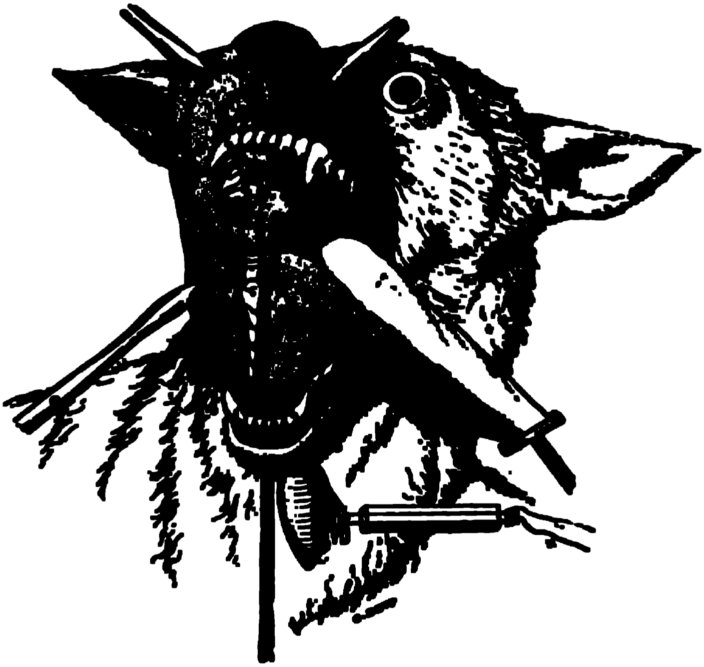
[10] Morat: "Physiol. of the Nerv. Sys.," transl. by Syers, p. 217, 1906.
[11] Morat: *Loc. cit.*, p. 218.



EFFECTS OF STIMULATION OF THE CERVICAL SYMPATHETIC. (*Morat*).

only should be affected is obviously due to the fact that each side has its own arterial supply derived from the corresponding carotid.

As to the supposed vasodilator properties of sympathetic nerves, Langley,[12] who, by the way, referring to the presence of such vasodilators, thinks it "premature to regard the question as settled," writes: "The strongest evidence for the presence of vasodilator fibers in the sciatic is that afforded by the series of well-known experiments initiated by Goltz,[13] on the effect of stimulating the sciatic nerve some two to four days after cutting it. The thermometric method, the plethysmographic method, and direct observation have given similar results, namely, that the vasoconstrictor action becomes less as time goes on, and that in the last day or two, before irritability completely disappears, the vascular dilatation is out of proportion to the preliminary contraction, or occurs without any contraction at all." But vasodilator sympathetic fibers are not needed to explain this phenomenon when we take into account the structural difference between motor and sympathetic nerves. The latter being relatively very thin, they are the first to degenerate and are soon unable to cause vasoconstriction. The motor nerve, being much larger, preserves its activity longer, and its function being, as a motor nerve, to cause stricto-*dilation*, this phenomenon may be produced after sympathetic has ceased to functionate. As everywhere else, the sympathetic acts as vasoconstrictor, while the motor nerve acts as vasodilator. Langley[14] concludes a comprehensive study of the subject by the statement that there is "no satisfactory evidence that the sympathetic sends vasodilator fibers to the skeletal muscles"—nor anywhere else, I would add.

Another supposed proof that the sympathetic can act as inhibitory nerve (of a function in this connection) is that of producing intense secretion of the sebaceous, lachrymal and Meibomian glands by dividing the nerve in the neck. But relaxation of the arterioles, and the consequent engorgement of the glandular elements, will produce this identical effect—

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[12] Langley: Schäfer's "T. B. of Physiol.," vol. ii, p. 626, 1900.
[13] Goltz: Archiv f. d. ges. Physiol., Bd. ix, S. 174, 1874.
[14] Langley: *Loc. cit.*, p. 641.

without in the least pointing to the presence of sympathetic "inhibitory" or "vasodilator" nerves.

This indicates that "inhibition" is not a function at all, and that what has been regarded as such is but an experimental phenomenon, and that the sympathetic has no "dilator" functions.

The "secretory" function of the sympathetic is poised on an equally weak foundation. Morat[15] writes: "In 1880, Luchsinger observed that stimulation of the cervical cord causes an abundant secretion of the sudoriparous glands in certain regions of the face (groin [snout] in the pig, muzzle in the ox), just as that of the dorso-lumbar sympathetic causes secretion of the glands of the hindlimb in the cat and dog. Czermak had already observed that stimulation of the cervical cord reacts on the submaxillary gland, causing a *very thick saliva* to flow from it; in both cases the motor or secretory nerves of the glands are put in action, this being another species of nervous action which may be added to the preceding." Again, "Cl. Bernard, in investigating the effects of the section of the cervical cord in the horse, had observed that the corresponding side of the face and neck was covered with sweat. But this phenomenon was then interpreted," remarks the author, "as being dependent on the vascular paralysis which follows this secretion. It is probable that it means something further, namely, the cessation of an inhibitory influence conveyed by the great sympathetic to the sweat-glands."

The supposed inhibitory influence of the sympathetic having proven to be an artificial phenomenon, as just shown, the opinion of Claude Bernard, that the sweating following division of the sympathetic was due to paralysis of the vessels, *i.e.*, to their passive relaxation, stands. Bernard's conclusion is not only sustained by my views, but it affords, moreover, the clue to secretory phenomena observed when the central end of the cut nerve is stimulated. Indeed, the fluid secreted differs from true saliva both in physical properties and quantity secreted. It is far more viscid, and, as shown by Heidenhain, the quantity secreted, both in dogs and rabbits, is very limited. "Unless the gland has been secreting under the influence of the cranial nerve [the chorda tympani], before stimulation of the sympathetic," writes Langley,[16] "this stimulation causes secretion of a few drops only, or it may be much less. Thus, in the dog, stimulation of the sympathetic for a minute will ordinarily produce two or three drops from the submaxillary gland, and perhaps half a drop from the sublingual." To call this a "secretion" requires, to say the least, considerable good-will, especially in view of the fact that if the sympathetic fibers are regarded as the vasoconstrictors of the glandular vessels, constriction of the latter by stimulating the cervical sympathetic suffices to cause the forcible projection, into the gland, of an excess of blood sufficient to account for the "saliva" secreted—a few drops of a serum-like fluid. In fact, if the vessels are allowed to relax and to fill again, the secreting process may be renewed at corresponding intervals. Thus, Langley writes: "The maximum total amount of saliva is obtained by stimulating the sympathetic for short periods, with short intervals of rest. Stimulated in this way—say, during every half-minute—the sympathetic will give from the submaxillary gland of the dog one-thirtieth to one-sixtieth of the quantity of saliva that would be obtained by similar stimulation of the chorda tympani."

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[15] Morat: *Loc. cit.*, p. 319.

Here, again, we are certainly not dealing with a secretory function, but with an artificial process. And this applies as well to Luchsinger's observation upon the snout of swine and the muzzle of oxen. By stimulating the cervical sympathetic, he caused excessive constriction of the smaller arteries and arterioles supplied by this nerve, and caused them to increase momentarily the work of the sudoriferous glands of the regions mentioned.

A brief review of the three main organs, the stomach, intestine and heart, in which the sympathetic is supposed to produce "inhibition" or carry on "secretory" or "motor" functions, will also show their true identity.

Secretory functions are ascribed to the sympathetic supply of the *stomach* by some investigators, in addition to those so conclusively shown by Pawlow to belong to the vagus. But Fremont[17] found that when the stomach was solely supplied by this nerve, *i.e.*, when both vagi had been divided, the secretion obtained was neutral and mucoid, and that it differed totally from the active gastric juice obtained when the vagi were whole, a fact which coincides with the experimental phenomena witnessed in the submaxillary gland. Pawlow[18] showed that division of the splanchnic nerve did not influence the character of the gastric secretion, thus indirectly sustaining Fremont's conclusion. Contejean[19] ascertained that in frogs, the sympathetic had but little influence upon the secretion. A similar conclusion was reached by Onuf and Collins[20] after experiments in cats. Nor are the movements of the stomach even governed by this nerve. Schiff taught that motor fibers were supplied by the sympathetic, and Morat "observed one case in which the rhythmical contractions of the stomach (and intestines) were augmented on stimulation of the splanchnics."[21] As a rule, however, he found that "excitation of these nerves caused diminution of the tonus as well as of the rhythmic contractions of the stomach." Starling[22] points to the trend of modern thought in this connection, when he says: "All observers, however, agree in describing the vagus as a motor nerve for the stomach."

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[16] Langley: Schäfer's "T. B. of Physiol.," vol. i, p. 495, 1898.
[17] Fremont: C. R. de l'Acad. de méd., Séance du 19 Nov., 1895.

It is clear, therefore, that the sympathetic is not the *secretory* nerve of the stomach, nor the *motor* nerve of its walls, and that the only nerve concerned with these functions is the vagus. On the other hand, the diminution of the tonus points clearly to excessive vasoconstriction—*i.e.*, to the vasoconstrictor rôle of the sympathetic.

Concerning the vasomotor innervation of the *intestine*, Langley[23] states that "nothing is yet known as to the nerve-cell connection of the cranial nerve-fibers to the gut," and, referring specifically to the sympathetic, the cranial and the sacral autonomic systems, says: "The relation of the enteric nervous system to those just mentioned is at present only a matter of guesswork." This state of things is plainly due to the misleading influence of excessive experimental vasoconstriction.

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[18] Pawlow: Archiv f. Physiol., S. 53, 1895.
[19] Contejean: Arch. de physiol. norm. et path., Oct., 1892.
[20] Onuf and Collins: Arch. of Neurol. and Psycho-Path., vol. iii, p. 2, 1900.
[21] Cited by Starling: Schäfer's "T. B. of Physiol.," vol. ii, p. 324, 1900.
[22] Starling: *Ibid.*, p. 322.
[23] Langley: *Ibid.*, p. 694.

The innervation of the intestine may be said to correspond with that of the stomach. Kaiser,[24] Ludwig, Ogata[25] and others have shown that the digestive process may proceed in the absence of the stomach. Now, Howell,[26] voicing the prevailing opinion, states that the fibers received from the sympathetic "give mainly an inhibitory effect when stimulated, although some motor fibers may apparently take this path." As "inhibition" means, in the light of foregoing facts, hyperconstriction of the arterioles, Howell's statement proves that the sympathetic supplies vasoconstrictor fibers to the intestine. Indeed, several investigators, including Betz, van Braam-Houckgeest,[27] Mall[28] and Starling,[29] found that anæmia "inhibited" all the movements of the intestines. Experimental diminution of blood in the intestinal vessels produces a corresponding effect. Thus, Starling states that if the aorta in the chest be obstructed, "there is a gradual diminution of intestinal tonus." . . . . "If now," adds this physiologist, "the blood be let in, the intestines contract immediately once or twice, then pause, and then recommence their rhythmic movements." This clearly shows that inhibition is due here, as elsewhere, to a deficiency of blood, whether the supply be reduced by excessive constriction of the intrinsic vessels or by obstruction of the afferent blood-stream at a remote spot.

While the sympathetic thus clearly asserts itself as the vasomotor nerve of the intestine, the true motor nerve of the intestine is as evidently the vagus: "The small intestine and the greater part of the large intestine," writes Howell,[30] "receive visceromotor nerve fibers from the vagi and the sympathetic chain. The *former*, according to most observers, when artificially stimulated, cause movements of the intestine, and are therefore regarded as the *motor* fibers."

All this does not mean that either the stomach or intestine are totally dependent upon their connections with the central nervous system either for their secretory or motor functions. Considerable testimony is available to show that they can autonomously secrete and undergo peristaltic movements, in virtue solely of their inherent irritability. Adrenoxidase is an important factor in this connection, since, as we have seen, the irritability of all cellular elements is governed by the activity of the interchanges of which they are the seat.

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[24] Kaiser: Czerny's "Beiträgen zur operat. Chirurgie," Stuttgart, 1878.
[25] Ogata: DuBois-Reymond's Archiv, p. 89, 1883.
[26] Howell: "Amer. T. B. of Physiol.," p. 364, 1900.
[27] van Braam-Houckgeest: Archiv f. d. ges. physiol., Bd. vi, S. 266, 1872.
[28] Mall: Johns Hopkins Hosp. Rep., vol. i, p. 37, 1896.
[29] Starling: *Loc. cit.*, vol. ii, p. 331.
[30] Howell: "T. B. of Physiol.," p. 646, 1905.

As to the *heart*, we have already seen that its coronaries are supplied with true vasomotor nerves, and I referred at the time to the fact that the large vessels differed from the smaller as to the source of the vasoconstrictor fibers, the sympathetic being an autonomous system. Indeed, the sympathetic gives rise to its own characteristic phenomena when, from any cause, it produces vasoconstriction of the terminal arterioles which it supplies. "It has long been known," write Brodie and Russell,[31] "that slowing of the heart or arrest of the heart can be brought about reflexly by excitation of almost any afferent nerve of the body if the stimulus be sufficiently great." Particularly sensitive in this connection are the abdominal viscera, especially, according to Tarchanoff[32] and François-Franck,[33] when these organs are inflamed. Goltz[34] found that tapping of a frog's intestines or stomach readily inhibited the heart. We have in the pugilistic "solar plexus" blow a familiar cause of reflex inhibition—not any more a physiological process than the supposed controlling influence of the vagus on the heart. The manner in which the sympathetic vasomotor terminals produce this reflex inhibition is suggested by the fact that Newell Martin[35] "found that stimulation of the vagus causes *dilatation* of the small arteries on the surface of the heart as seen through the hand lens." "Moreover," writes Howell[36] in this connection, "when the heart is exposed and artificial respiration is stopped, the arteries may be seen to dilate before the asphyxia causes any general rise of arterial pressure." These results are readily accounted for when it is borne in mind that the sympathetic fibers are distributed only to the terminal arterioles. The two exciting agents (toxic wastes due to hypocatabolism when artificial respiration ceased, as to the second cause), by causing constriction of these terminal vessels, obstruct their blood-stream, and cause the latter to expand the vessels *behind* the seat of obstruction.

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[31] Brodie and Russell: Jour. of Physiol., vol. xxvi, p. 92, 1900.
[32] Tarchanoff: Arch. de physiol. norm. et path., T. ii, 2 série, p. 496, 1875.
[33] François-Franck: Trav. du Lab. de Marey, ii, p. 221, 1876.
[34] Goltz: Virchow's Archiv, Bd. xxvi, S. 1, 1863.
[35] Newell Martin: Trans. Med. and Chir. Faculty of Maryland, p. 291, 1891.
[36] Howell: "T. B. of Physiol.," p. 550. 1905.

This brings us to the specific functions of the sympathetic terminals. Howell,[87] in his review of the tonic activity of vasomotor nerves, says: "Normally, the arteries—*that is, the arterioles*—are kept in a condition of tone by impulses received through the vasoconstrictor fibers." He evidently means sympathetic fibers, for all the examples he cites refer to stimulation of sympathetic nerves. Moreover, Hall, in accord with all other physiologists, states that the smaller arteries and *arterioles* are supplied with sympathetic vasoconstrictor fibers. Now, Howell writes: "When *vasoconstrictor fibers* are stimulated there is a *rise* of blood-pressure in the *artery* supplying the organ and a *fall* of pressure in the *veins* emerging from the organ. This result is what we should expect if the constriction takes place in the region of the arterioles." This clearly identifies the sympathetic with the function of the organ, and suggests that it influences in some way the *volume* of blood admitted into it.

The need of such a regulative factor almost imposes itself in view of the following additional statements by Howell: "The capillary region, including the smallest arterioles and veins, offers a great resistance to the flow of blood, and this resistance is spoken of as the *peripheral resistance.* Its effect is to raise the pressure on the arterial side and lower it on the venous side. When other conditions in the circulation remain constant it is found that an increase in peripheral resistance, caused usually by a constriction of the arterioles, is followed by a rise of arterial pressures and a fall of venous pressures. On the contrary, a *dilatation of the arterioles* in any organ is followed by a fall of pressure in its artery or arteries and a rise of pressure in its veins." This quotation repeats, in a measure, the contents of the foregoing paragraph. If, however, the two are carefully compared, a salient feature will assert itself, namely, *it is the sympathetic fibers supplied to the arterioles which govern peripheral resistance and that, therefore, peripheral resistance is governed by the sympathetic center.*

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[87] Howell: *Ibid.*, p. [illegible].

The far-reaching importance of this function will now assert itself. Osler[28] remarks: "Tissue irrigation is primarily from the heart, but in all extensive systems of this sort, provision is made at the local territories for variations in the supply, according to the needs of a part. The sluices are arranged by means of the *stop-cock action of the arteries*, which contract or expand under the influence of the vasomotor ganglia, central and peripheral. If the sluices of one large district are too widely open, so much blood may enter that other important regions have not enough to keep them at work." Now, this "stop-cock action of the arteries" cannot be accounted for when the vasomotor system *per se* is considered as the mechanical factor in the process, since constriction of the larger vessels would overcome that of the smaller into which they drive their blood. The body is, therefore, as I have shown in the sixteenth chapter, provided with an autonomous vasomotor system, the sympathetic, which presides solely over this "stop-cock action." The ganglia to which Osler refers are, in fact, as every one knows, the sympathetic ganglia.

This "stop-cock action" has a specific purpose in this connection, however, namely, that of *enforcing the resumption of their normal caliber to the small vessels and arterioles after dilation by the stricto-dilators.* Through this rôle, sympathetic fibers take an active part in all organic functions, as will now be shown.

In the eighteenth chapter I submitted the evidence which had led me to conclude (1) that an exacerbation of activity in any organ was the result of the admission into it of an excess of blood over and above that circulating through it during repose; (2) that this was brought about by dilation of the arteries which admitted the blood into this organ; (3) that this dilation was due to diminution of adrenoxidase in the walls of these arteries and the resulting hypocatabolism therein; and finally (4) that this was accomplished by cranial motor-nerve terminals distributed to the vasa vasorum or capillaries which nourished these vessels.

Now, this "stricto-dilation" of the supply arteries may well be compared to turning on of the blood-stream by opening the stop-cock. It is obvious, however, that so important a function as the resumption by the dilated arterioles of their normal caliber, *i.e.*, to a degree of contraction exactly adapted to nutrition and just short of functional activity, cannot be left to so uncertain a process as passive dilation. Nor can it be left to the fibers of the vasomotor system, for this would entail constriction of the larger arteries of the body also, and, by forcibly dilating the small arteries of the organ, defeat the object in view. But this object is fulfilled by terminal fibers of the sympathetic which provoke vasoconstriction of the arterioles. They reduce the volume of blood admitted into the organ during active function—partly turn off the stop-cock, as it were (not entirely, since this would cause arrest of function, *i.e.*, inhibition), and cause the organ to resume the passive state—a condition in which it is ever ready to become active when the stream of blood passing through it is again enlarged through the vasodilator impulses of the stricto-dilators.

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[28] Osler: "Pract. of Medicine," p. 718, 1905.

The schematic illustration shown herewith represents in Figs. 1 and 2 the mechanism through which an arteriole is dilated by the stricto-dilators, which are fibers of a *cranial* motor or secretory nerve (the vagus, facial, etc.), during function; and then restored to the passive state by the sympathetic vasoconstrictor fibers. This accounts for the fact that the sympathetic center is located, as I pointed out in the sixteenth chapter, in the same organ to which I had traced the cranial nerves, *viz.*, the posterior or neural lobe of the pituitary body. The purpose of this intimate relationship is self-evident, now that we have seen that the functions of all organs are carried on by the joint action of the terminals of a cranial and sympathetic nerve.

Briefly, it appears to me: (1) *That the sympathetic system does not, as now believed, carry on motor, dilator, secretory, or inhibitory functions;* (2) *that its function is purely vasoconstrictor, its field being limited to the small arteries or arterioles;* (3) *that it is entirely independent of the vasomotor system (whose action is general), being capable, unlike the latter, of influencing each organ individually;* (4) *that its terminals form part of the mechanism of all organs;* (5) *that the specific rôle of its terminal fibers is to oppose the stricto-*

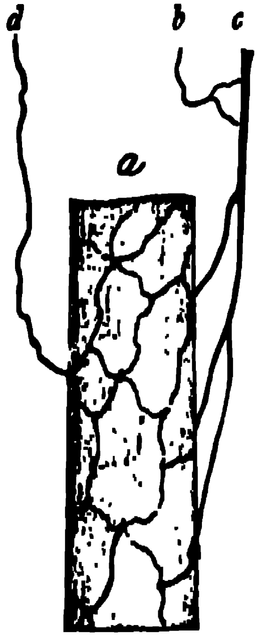

Fig. 1.

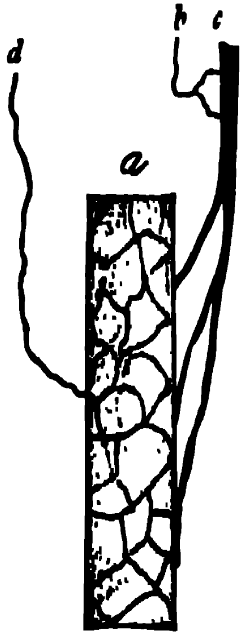

Fig. 2.

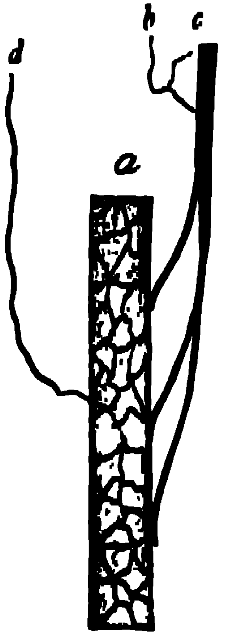

Fig. 3.

SCHEMA OF THE STRICTO-DILATOR (CRANIAL-MOTOR) AND SYMPATHETIC NERVES IN THEIR RELATIONS TO ORGANIC FUNCTION.

[illegible]

Fig. 1. DURING FUNCTION: *Arteriole a* dilated; stricto-dilator b active and vasa vasorum c constricted; sympathetic d passive.

Fig. 2. DURING REST, organ being kept nourished: *Arteriole a* semi-contracted; stricto-dilator b passive and vasa vasorum c dilated; sympathetic d active.

Fig. 3. DURING INHIBITION (excessive and therefore morbid constriction), the organ being deprived of blood: *Arteriole a*, lumen obliterated; stricto-dilator b passive and vasa vasorum c dilated; sympathetic d over-active.

dilators and restore the arterioles of an organ to their normal caliber when the functional activity of that organ is to cease; (6) *that the volume of blood which circulates through any organ, whether the latter be in the passive state or functionally active, is regulated by the joint action of the motor and sympathetic centers in the posterior pituitary;* (7) *when the organ is to become functionally active, the stricto-dilators cause its vessels to relax and to augment the volume of blood coursing through it; when its activity is to cease, the sympathetic constrictors cause the vessels to contract sufficiently to reduce the blood in transit to the volume required for adequate local nutrition.*

The conjoined action of the sympathetic and cranial terminals subserves another rôle of special importance in pathology and therapeutics.

That the sympathetic fibers distributed to the arterioles serve to maintain their tone is a recognized fact. It becomes a question, however, whether so simple a mechanism meets the needs of the functions these small vessels must perform. The blood they transfer into the capillaries meets therein very great resistance, not only in the skin, the familiar "peripheral resistance," but in all organs. The diffusion of the blood-plasma through the endothelial walls of the capillaries is so closely interwoven with the vital process itself that the need of a mechanism to regulate the pressure in the capillaries almost imposes itself. The regulation of the surface temperature, so important to the well-being of the entire organism, also seems to require the presence of a local mechanism capable of adjusting the cutaneous circulation to the needs of the moment. Blushing, which under the influence of emotion may occur suddenly and last as long as the emotion lasts, betokens the presence of something more than a system of fibers calculated to sustain vascular tonicity, especially when peripheral resistance is taken into account. The flushings of menopause, the "heat-waves" of various disorders, localized inflammation, etc., all of which occur irrespective of any general febrile state and fever itself, are but examples of many patho-physiological phenomena which point in the same direction.

All the evidence submitted in the foregoing pages not only affords additional testimony to the effect that a more important mechanism is present at the threshold of the capillary system than has as yet been discerned, but it indicates a close parallelism between the physiological rôle of the heart and that of the arterioles. The heart's innervation consists likewise of cranial and sympathetic filaments by which the organ's contractile power and rhythm are regulated. Like the arterioles, it has great resistance to overcome, and does it by periodical muscular contractions—dilation to admit the blood it is to distribute through the arteries, constriction to project it into these vessels. Briefly, the arterioles, considered in this light, are, like the heart, contractile muscular organs which, owing to their contractility (governed by cranial and sympathetic nerves through impulses received from their respective centers in the posterior pituitary), are able to project and actually *propel* the blood with sufficient vigor to overcome resistance. While the heart impels its blood into the arteries, the arterioles project theirs into the capillaries—pumping each wave in, as it were.

We have striking examples of such a function in many lower forms, *i.e.*, animals in which a vessel may even fulfill the functions of a heart. "In the various groups of worms there are many which possess a very elaborate vascular system," writes Willey, "while not one of them possesses a heart. In fact, in the last mentioned forms, the place of a heart is taken, functionally, by *contractile blood-vessels*. And this is the case with Amphioxus"—a lively little animal, as any one knows who has handled it.

The manner in which the blood streaming through the arterioles is further propelled by the contractions of these vessels at each pulsation, suggests itself when a peculiarity in the structure of the muscular coat of these small arteries is taken into account. Berdal[388a] states that "muscle-cells form a single and continuous layer around the small vessel" and that "they are wrapped *spirally* around the arteriole." This is shown in the annexed plate. That they receive nerve-fibers, *i.e.*, sympathetic filaments, we have seen. Now, nerve-impulses to muscle-cells so disposed around a vessel, cause not only constriction, but also

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[388a] Berdal: "Histologie Normale," p. 367, 1894.

—the contraction starting from the inner end of the spiral muscle and proceeding toward the capillary—centrifugal propulsion of the blood. This mechanism, which may be likened to that of a tight ring slid along a flexible tube, is a counterpart of that to which the propulsion of food-stuffs in the intestinal canal is due. Indeed, this parallelism appears to me very suggestive, since the intestines and arterioles represent in reality the extremities of the alimentary system: the intestines for the admission of food materials, and the arterioles for their distribution to the tissues.

As a corollary to the foregoing conclusions, I would suggest, therefore: (1) *that the cranial and sympathetic filaments distributed to the arterioles carry on an additional and more important function than that of maintaining their tonus;* (2) *that these nerves, owing to the presence in the walls of the arterioles of spirally disposed muscles, endow these vessels with a special property: that of increasing the vis a tergo motion of the blood in order to overcome the resistance of the capillaries.*

DRUGS WHICH PROMOTE THE FORMATION OF AUTO-ANTITOXIN AND INCITE AN ARTIFICIAL FEVER BY EXCITING THE VASOMOTOR AND SYMPATHETIC CENTERS.

"Since the researches of Claude Bernard, of Vulpian, of Kölliker," writes Richet,[30] "the term 'curarizing poisons' is given to many substances which, like curare, abolish the action of motor nerves upon muscles. The action of these substances," adds this eminent physiologist, however, "is hardly better known than that of curare itself. It is generally admitted that it is upon the intramuscular terminals that these poisons elect to attack; but we are far from being informed as to the modifications of which they are the seat." The list of the poisons referred to includes the alkaloids of drugs in general use, atropine, aconitine and brucine, for instance.

As interpreted from my standpoint, the prevailing belief that these drugs act directly upon the nerve-endings is erroneous and misleading.

That a motor nerve augments the volume of blood supplied to an organ, and thereby incites functional activity, was shown by Claude Bernard. Indeed, as emphasized by Arnold, Brown-Séquard, Budge, and recently by Jacques Loeb,[40] ganglia and nerves serve only to increase the inherent sensitiveness of a given structure by enhancing, through a greater blood supply, its intrinsic metabolism. I have just pointed out how this is accomplished, viz., by stricto-dilation of the arterioles of an organ. We have seen, moreover, that when the functions of this organ are to cease, the sympathetic fibers distributed to the muscular layer of its arterioles cause the latter to contract.

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[30] Richet: *Loc. cit.*, p. 632.

The effects of curare—and of the many poisons it exemplifies—are no longer obscure when this mechanism is taken into account.

It is now claimed that the classical experiments of Claude Bernard and Kölliker, in which ligation of the arteries of one leg protects it from the effects of the poison, prove that curare acts directly upon the peripheral tissues and not primarily on the central nervous system. This claim is unfounded, however, in the light of my views, since the immunity of the leg referred to can be explained in another way. Thus, if the injected curare, by acting directly upon the *sympathetic center*, were to cause sufficient constriction of the arterioles of the leg-muscles, ligation of the artery of that leg would also annul the effects of the poison in that leg, since the resulting ischæmia of the walls of the arterioles below the ligature would prevent the marked constriction of the sympathetic terminals, which causes paralysis by blocking the circulation to the nerve terminals, the muscles, etc. The poison, by irritating the central origin of the nerves to the arterioles, would thus paralyze all the muscles of the body with the exception of those of the limb, as observed experimentally.

As we will see, this general principle is applicable to many drugs, including anæsthetics and analgesics. In the case, at least, of some of the latter, the action on the sympathetic center is of such importance that the peripheral effects are arrested experimentally by section of the basal or spinal paths through which sympathetic impulses are transmitted.

Richet also says, however: "Nerve-cells are exceedingly varied, and the various poisons do not exert the same action upon them. There are special affinities by this or that nervous element, for this or that poison. Atropine will fix itself upon the nerve-terminals of the motor cells of the third or tenth pair; curare, upon the motor nerves of vegetative life; muscarine, upon the cardiac ganglia; digitaline, upon the bulbar cardiac centers; cocaine, upon the sensory terminals of nerves." While the fact that the *local* application of the drugs referred to produces these effects, such is not the case (in the light of my views) when they are administered orally, subcutaneously or intravenously; all the "curarizing" drugs act in the manner specified above, viz., by exciting the sympathetic center, either alone or as one of the *centers* of a group for which the drug may have special affinity—precisely as it has for peripheral nerve-cells when applied topically.

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[40] Jacques Loeb: *Loc. cit.*, p. 32.

The action of a drug upon the *vasomotor center*—affecting through it the larger vessels—is shown in the following experiment related by Leonard Hill:[41] "By the injection of essential oil of absinthe in a curarized animal, the vasomotor center can be excited to the discharge of a succession of powerful spasms, by each of which the *arterial pressure* is driven up *to a great height*. This phenomenon suggests a clonic fit of the center, the clonus of involuntary muscle naturally taking place at a far slower rate than that of skeletal muscles." It is evidently the action of the vasomotor center alone which caused the great rise of pressure, since—interpreted from my viewpoint—the curare had already excited the sympathetic center, producing excessive constriction of the arterioles and (what is now believed to be paralysis of the nerve terminals directly by the poison) ischæmia of the nerve-endings and arrest of their functions. The great rise of blood-pressure itself thus becomes a normal result of the obstruction presented by the constricted arterioles to the blood projected towards the periphery by the deeper and greater vessels which are themselves constricted, but through impulses from the vasomotor center. An important feature is emphasized by these facts, viz., that the vasomotor center can be stimulated independently of the sympathetic center, and *vice versa*.

These two centers may even be caused to antagonize each other. Thus, as stated by Stewart,[42] a small dose of atropia, given hypodermically, "abolishes the secretory action of the chorda tympani." He also says, however, that "pilocarpine is the physiological antagonist of atropia, and restores the secretion which atropia has abolished," as first shown by Langley. Now, after atropia, by stimulating the sympathetic center, has caused hyperconstriction of the arterioles, the chorda tympani can no longer increase the flow of saliva when excited, because the arterioles are *kept* constricted by the sympathetic constrictors. This is overcome by pilocarpine, however, because it causes (1) "after a few moments," as stated by Wood,[43] "the characteristic phenomena of a slow pulse with increased arterial pressure"—which means that it excites powerfully the vasomotor center, the slowing of the heart being due to the increased resistance of the blood-column. This provides a mechanical agent capable of enforcing relaxation of the constricted arterioles: the centrifugal pressure of the blood projected into it by the deeper contracting arteries.

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[41] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 139, 1900.

We thus have two centers acting individually, *sympathetic* and *vasomotor*, and peripheral effects which require no local action of the drugs to account for them. If we now add the *adrenal center*, influenced through the test-organ, and the reaction of which to toxics has already been shown, we have three centers which (simply because of their identity as the most highly organized sensitive structures of the body) are stimulated—or better, irritated—by certain agents, several of which are among our time-honored remedies.

The remedies studied in the present chapter will include those which, besides calling forth a reaction of the test-organ and through it increased functional activity of the adrenal center, excite (as a foreign constituent of the blood) either the sympathetic center or the vasomotor center. It will be shown that in each case the specific action of the drug is accounted for through the *combination of centers* affected, and the degree of irritation to which the drug submits each of them. Although the latter are always placed in evidence, and the data submitted, in accord with recorded experimental evidence, point to them as the nervous elements (owing to their greater inherent sensitiveness) most actively excited by the drug, it is possible that in the case of some agents, strychnine for example, the subsidiary centers of the cord, bulbar and spinal, may be likewise excited as they are in the lower vertebrates, the frog, for instance. This applies mainly, however, to those drugs which affect the vasomotor (bulbar) center. In drugs of the coal-tar series, such as antipyrin and other antipyretics, for example, all effects cease when the base of the brain is transected far above the bulb and immediately in front of the pituitary body—the organ which contains the adrenal and sympathetic centers.

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[42] Stewart: "Manual of Physiol.," p. 347, 1900.
[43] Wood: *Loc. cit.*, thirteenth edition, p. 724, 1906.

A salient fact asserts itself in this connection, however, *viz.*, that drugs administered internally invariably affect nerve-cells of the spinal system only. There is no tangible proof in support of the prevailing belief that drugs, belladonna and cocaine, for instance, produce delirium by acting directly on the cerebral nerve-cells; while, conversely, there is ample evidence to the effect that hyperæmia of these cells—especially in view of the fact pointed out by myself that adrenoxidase-laden plasma circulates in nervous elements as it does in all other cellular elements—can provoke this symptom. Hyperæmia is purely a motor phenomenon, *i.e.*, an excess of blood driven into the brain by excessive vasomotor activity. We have in the cutaneous hyperæsthesia produced by corresponding drugs, not only evidence to this effect, but proof that the sensory elements—such as those of which the *entire* cerebrum is composed—(though capable of transmitting impulses to the cord which therein awaken motor stimuli) can be rendered overactive by a supranormal supply of blood.

On the whole, in the light of my views, (1) *drugs administered by the mouth or hypodermically produce none of their effects by acting directly on peripheral structures, including the cerebrum, heart and cutaneous sensory nerve organs;* (2) *they invariably do so by stimulating or depressing one or more centers in the spinal system. and particularly, and in many instances solely, those located in its chief center, the .posterior pituitary body.*

The drugs reviewed in the present chapter are those which

—as I interpret their physiological action—stimulate the three centers referred to—all of which influence the body at large. When stimulated by either of these drugs, the *sympathetic center* reacts in its own specific way. In other words, it is the function of the sympathetic terminals to regulate the tonus of the arterioles, *i.e.*, their mean caliber during their dilation and contraction at each pulsation, and it is this function that they exaggerate when their center is excited: they reduce this mean caliber. At first, however, or when small therapeutic doses are given, this serves only to *increase the propulsive activity of the arterioles*, for the abnormal narrowing of these vessels is followed by their *reflex* dilation (stricto-dilation from my viewpoint)—a generally recognized function, the increase of the propulsive power being due to the fact that both dilation and contraction of the vessels are exaggerated. Gradually as the dose is increased, however, the sympathetic stimuli become so energetic that the arterioles are kept constricted, the vasodilator reflex action being increasingly overpowered. Finally, their constriction becomes such that their lumen is obliterated, a condition which entails death by arrest of the circulation in the heart muscle.

The drugs which excite the *vasomotor center*, by provoking constriction of the larger and deeper vessels, force an increased volume of blood towards the periphery. The arterioles may not only remain passive under these conditions, but they may be forcibly dilated by the centrifugal streams, and the blood invade the tissues. The symptoms of excessive hyperæmia witnessed, cerebral, muscular, etc., are but normal results of such a process.

The drugs reviewed in the present section are all able more or less actively to excite the test-organ, and thus to increase, through the *adreno-thyroid center*, the volume of adrenoxidase and thyroidase produced. This means that they can enhance the protective properties of the blood by augmenting its proportion of auto-antitoxin. The main subjective phenomenon awakened is a rise of temperature, the adrenal center being, as I have shown, the heat or thermogenic center. Although the adrenal center is alone mentioned in this connection, it is because the only phenomena in evidence are traceable only to this center. That its "thyroid" moiety is also active is probable, however, since an increase of adrenoxidase involves a corresponding increase of all its constituents, including thyroidase.

The effect produced by the simultaneous excitation of various combinations of these three centers can be best illustrated by an outline of the mode of action of the various drugs treated in this chapter. It will serve to show, moreover, that notwithstanding the simpler explanation of their action which I submit, the specific action of each drug remains clearly defined.

The physiological action of *belladonna* and *atropine* illustrates the joint action of the adrenal and sympathetic centers. A protective reaction of the test-organ being provoked, the blood is rendered richer in adrenoxidase and therefore in auto-antitoxin. The sympathetic center being simultaneously excited, the propulsive activity of the arterioles is enhanced and an unusual quantity of blood rich in adrenoxidase and auto-antitoxin is thus projected into the capillaries of all organs. Hence the cutaneous hyperæmia and other symptoms observed. The beneficial effects thus become plain: it initiates an artificial fever, and enhances circulatory activity in exposed organs. Its toxic effects become manifest through the sympathetic center, the result being excessive constriction of the arterioles of the heart and anterior pituitary, the circulation in these organs becoming inadequate to sustain life.

Digitalis likewise stimulates the two centers affected by belladonna. Indeed, like atropine, digitaline in large doses causes dryness of the throat, dilation of the pupil, hallucinations, etc. Digitalis differs from belladonna, however, in that it excites much more actively the adrenal center, and with less vigor the sympathetic center. The blood is thus not only made richer in adrenoxidase and other substances which sustain metabolism and nutrition, but, the center which governs the propelling power of the arterioles being activated, the nutritional elements are driven into the tissues, including the vascular and cardiac muscle, with unusual vigor. The energy with which digitalis excites the test-organ, and through it the adrenals, manifests itself in another way: the direct action of the excess of secretion on the right ventricle. So marked is this action that large doses disturb the synchronism of the two ventricles. It is through both the arterial and venous blood it receives that the heart's power is increased and sustained by adequate nutrition.

Nux vomica and *strychnine* introduce another combination: stimulation of the adrenal center (through the test-organ) and of the bulbar vasomotor center. Here, the metabolic activity of all organs and their nutrition is likewise enhanced, but instead of activating the sympathetic center which increases the propulsive power of the arterioles, strychnine excites the vasomotor center only, and by thus provoking constriction of the deeper vessels, it causes a greater volume of blood to circulate in the smaller vessels and capillaries. Therapeutic doses, therefore, thus transfer to the arterioles an unusual quantity of blood—and thereby enable these small vessels to nourish the tissues more actively. When large doses are given, however, the stream forcibly dilates the arterioles, and highly oxygenized blood invades the cerebro-spinal system, the muscles, the skin, etc., in such quantities that convulsions occur.

Coca and *cocaine* assert themselves as more powerful stimulants of the test-organ and adrenal center than either belladonna, digitalis, or strychnine. The resulting marked increase of adrenoxidase in the blood not only augments correspondingly the activity of all metabolic processes, but as both coca and cocaine, like strychnine, excite the bulbar vasomotor center, this blood is projected in greater quantity into the arterioles, and, therefore, into the tissues. The characteristic effect of coca on the muscular system is due mainly, therefore, to its very marked action on the adrenal center, sustained by the rise of vascular tension, which floods, so to say, the muscular elements with highly oxygenized blood. The kinship with belladonna is shown by the fact that it causes, in large doses, dilation of the pupil, dryness of the mouth and throat, etc.; with digitalis, by its powerful action on the heart-muscle; and with strychnine, by its marked action on all muscles and its tendency in toxic doses to produce convulsions, the so-called "cocaine epilepsy."

Quinine introduces a different phase of action, *viz.*, irritation of an increasing number of centers as the dose of the drug is increased. Thus, when given in therapeutic doses, it excites the vasomotor center, causing peripheral hyperæmia; larger doses excite the sympathetic center besides; still larger doses excite the test-organ in addition to the two others, and through it the adrenal center. The effects produced thus begin with slight cutaneous warmth and hyperæsthesia, and gradually, as the dose is raised, increase to headache, flushing, tinnitus, etc., and then, in some cases, to a marked rise of the temperature. The latter effect is shown to be due to the specific property which quinine shows prominently in malaria, *i.e.*, a direct toxic action upon certain parasites, including the plasmodium malariæ—but, unfortunately, the leucocytes also. This action is exercised irrespective of the influence of the drug upon the various centers, but the latter assists materially the curative process by causing a greater volume of blood to circulate in the capillaries—which include those of the liver and skin—thereby bringing about an artificial febrile process in which the quinine acts as the body's immunizing agent.

That these simplified conceptions of the physiological action of these various drugs are sound, is shown by the fact that in every instance the indications they suggest in the many diseases in which they are used harmonize perfectly with the teachings of clinical experience.

IDIOSYNCRASY.—This term is applied to the marked susceptibility shown by many persons to the action of various drugs. The cause of this phenomenon becomes evident when, in accord with my views, nerve-centers are regarded as the structures directly irritated by drugs. In the first volume I referred to the posterior pituitary body as the *sensorium commune, i.e.,* as the organ through which all violent emotions, shock, surgical shock, etc.—and to which I may add another obscure phenomenon, concussion, react upon the organism at large, all owing to the extreme sensitiveness of its highly organized centers. That blood contaminated by irritating drugs, poisons, toxins, etc., in circulating in the nervous elements of such an organ, should readily excite these elements is self-evident. That such blood should not excite these centers to the same degree in all individuals, however, is as obvious; it is here that, in my opinion, the secret of idiosyncrasy lies, viz., in *an abnormal sensitiveness* *of the nerve-centers upon which drugs act, and particularly the sympathetic center.*

This feature of the problem is illustrated by the action of some of the drugs studied in the present and in the next chapters.

BELLADONNA AND ATROPINE.

Physiological Action.—Belladonna and its alkaloid, atropine, owe their therapeutic properties to the fact that they stimulate (1) the test-organ (anterior pituitary), and through it the adrenal center;* and (2) the sympathetic center (posterior pituitary), which governs the tonus and propulsive activity of the arterioles.*

The experiments of Lombard,[44] confirmed by Calmette,[45] have shown that the leucocytes ingest atropine injected in the blood, and that the latter itself contains but a very small proportion of the poison. As these cells ultimately secrete their contents, the drug is doubtless returned to the circulation, as is the case with other drugs. The influence of the drug upon the test-organ and adrenal center (which is also the heat or thermogenic center) is shown by its marked influence upon the temperature. Thus, Meuriot[46] observed, in man, an elevation of temperature ranging from 0.5° to 1.1° C. (0.9° to 2° F.) after the use of therapeutic doses, and refers to Eulenburg as having made a similar observation. He also obtained in dogs, from doses corresponding with the equivalents of therapeutic doses in man, a rise of from 1° to 3° C. (1.8° to 5.4° F.) and alludes to Duméril, Demarquay and Lecointe as having caused a *rise* of 4° C. (7.2° F.) after *small* doses, and a *fall* of 3° C. (5.4° F.) after *toxic* doses. That this rise is due to excitation of the adrenal center, where I located the heat-center, is shown by the experiments of Ott and Collmar,[47] who found that the rise of temperature occurred irrespective of the variations of blood-pressure, and ascribed it, therefore, to a stimulating action of the drug on the thermogenetic centers. Again, we have seen that excitation of the test-organ, and through it the adrenal center, caused glycosuria; now Raphaël[48] not only observed glycosuria when atropine was used experimentally, but also in individuals under the influence of large doses.

The action of atropine upon the vascular mechanism is generally recognized. That it is the arterioles which are mainly influenced (since all vessels are to a certain degree constricted through the presence of an excess of adrenoxidase in the blood) is shown by the fact that toxic doses produce arteriole hyperconstriction, *i.e.*, "inhibition." Thus Bezold and Bloebaum[49] found that when large doses of atropine were injected into the brainward blood-stream, *i.e.*, the carotid, the heart was at once greatly slowed. That this is due to paralysis of the heart through deficient blood supply is shown by Cushny's statement,[30] that large quantities of atropine "weaken and depress the heart muscle, and the contractions consequently become slower and weaker, and the output of the heart is less than normal."

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* *Author's conclusion.*

[44] Lombard: Thèse de Paris, 1901.

[45] Calmette: Cited by Labbé: *Loc. cit.*

[46] Meuriot: Thèse de Paris, 1868.

[47] Ott and Collmar: Therap. Gaz., Aug., 1887.

[48] Raphaël: Deut. med. Woch., Bd. xxv, S. 451, 1899.

[49] Bezold and Bloebaum: Untersuchungen aus der physiol. Lab. zu Würzburg. B. I.

The central origin of all the phenomena produced by belladonna and atropine is demonstrated by the fact that Bezold and Bloebaum[31] found transection of the upper portion of the spinal cord annulled its action on the blood-pressure, a fact confirmed by Wood.

By its action on the test-organ and adrenal center belladonna increases the proportion of adrenoxidase in the blood, while by its action on the sympathetic center, it enhances the blood-propelling power of the arterioles.* As a result, the capillaries of the entire organism are traversed by a supranormal quantity of arterial blood unusually active in oxygenizing properties.* Hence the sensation of warmth in the skin and mucous membranes, and the rise of temperature and transient flushing, observed even when small doses are taken.* This is soon accompanied by dryness of the throat, owing to capillary engorgement of the acini in the latter and of the sudoriferous glands in the skin, and mechanical interference with their functions.

When the dose is large, various symptoms due to hyperæmia and hypermetabolic activity in the organs influenced* are witnessed. Thus, a bright red flush, recalling that of scarlatina, though more diffuse, may appear on the face and gradually involve the entire surface. Slight congestive headache, with giddiness, insomnia, mental confusion, garrulousness with illusions, delirium, which may become violent, visions, etc., are also observed, along with, in some cases, priapism, muscular restlessness and forcible micturition, due to more or less sudden involuntary contraction of the bladder. The pulse-rate is also greatly increased, and the cardiac contractions (unless toxic doses be taken) strong, owing to similar overactivity of the cardiac muscle.*

Cushny[32] states that the cause of the rise of temperature induced by atropine "cannot be said to be definitely known." The presence of an excess of adrenoxidase in the blood, coupled with the capillary engorgement, as previously explained, accounts not only for this phenomenon, but also for the familiar symptoms outlined above. The concurrence of the pyrexia with cutaneous disorders is plainly shown in all cases attended with untoward effects. In a case brought on by the use of atropine as a mydriatic, observed by Spurgin,[53] for instance, a diffuse rash resembling that of scarlet fever, observable also in the fauces, coincided with a temperature of 102.7° F. and a pulse-rate of 140. In another instance reported by the same observer, the cutaneous lesions were not quite as marked, the temperature was 101.3° F. and the pulse-rate 116. In both cases the morbid symptoms disappeared on discontinuing the use of the drug.

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* *Author's conclusion.*

[30] Cushny: *Loc. cit.*, fourth edition, p. 236, 1906.

[31] Bezold and Bloebaum: *Loc. cit.*

[32] Cushny: *Loc. cit.*, fourth edition, p. 238, 1906.

The mydriatic action of atropine is due to a corresponding process when the drug is given internally.* Here, however, there are two sets of muscles: the constrictor fibers, which cause contraction of the pupil, and the dilator fibers, which act in the opposite way. As both muscles are rendered overactive by the excess of arterial blood rich in adrenoxidase propelled into them by the arterioles, the delicate muscular equipoise which enables the pupil to carry on its functions is lost and it becomes a question as to which of the antagonistic muscles will overcome the other.* The radiating fibers being best disposed mechanically (owing to direct traction),* they draw back the edges of the iris, enlarging the pupil.

The local application of atropine produces the same effect, but in a different way.* It paralyzes directly the sympathetic terminals* of the arterioles, thus causing dilation of these vessels. An excess of blood being admitted to the muscular elements of the iris,* the antagonistic action of the muscles is awakened* and the radiating fibers cause dilation of the pupil by drawing back the iridial curtain.

Landois (1905) concludes[54] that "as to the action of poisons on the iris [including atropine] ignorance still prevails." The greater contractile power of the radiating muscles when the functional equipoise between the two sets of muscles is disturbed is well shown by the observations of Bernstein and Dogiel, confirmed by Engelhardt,[55] that when electrodes were applied "to the eyes in such a way as to affect directly the iris, contraction occurred."[56] Again, the dependence of the process upon some difference in the relative power of the antagonistic muscles is suggested by the fact that in birds and reptiles atropine does not cause dilation of the pupil (Wharton Jones, Ivanoff, Wood and others).

The muscular antagonism and the participation of the sympathetic in the process are shown by the following lines by Cushny:[57] "A further question is whether this [paralysis] is the only effect of atropine on the pupil, or whether the terminations of the dilating *sympathetic fibers* are not *stimulated* at the same time, and this cannot as yet be said to be generally agreed upon, although there is very strong evidence against the latter view. Its advocates have generally ignored the *fact* that the constrictor muscle is constantly opposed by dilator fibers, and that when the former is thrown out of activity by the paralysis of the terminations of the motor oculi, the radiating fibers cause an *active* dilatation without any stimulation of the nerve ends being necessary." The prevailing misinterpretation of the functions of the sympathetic and the multiplicity of functions erroneously attributed to this nerve account for the vulnerability of the views Cushny criticizes. If, setting aside assumptions, we accept the only actually demonstrated function of sympathetic terminals, that of constricting arterioles, as a foundation for deductions, the ground for criticism disappears, since the only solidly established fact concerning the *local* action of atropine, paralysis of nerve-endings, also comes into play. By paralyzing the sympathetic constrictors, therefore, the vessels are allowed to relax and to influence the muscular fibers differentially—a process which necessarily brings in the antagonistic action of the muscular fibers of iris referred to by Cushny. The hyperæmia produced by the dilation of the arterioles not only accounts for the dilation of the pupil, but the fact that hyperæmia is likewise the mode of action when atropine is given internally, and that the phenomenon is explained by a process provoked by the drug in all other organs, indicates that the explanation I submit must be the correct one.

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* *Author's conclusion.*

[53] Spurgin: Lancet, Sept. 30, 1905.

[54] Landois: *Loc. cit.*, p. 843, 1905.

[55] Engelhardt: Untersuchungen a. d. physiol. Lab. zu Würzburg, ii, S. 221.

[56] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 177, 1906.

[57] Cushny: *Loc. cit.*, fourth edition, p. 264, 1906.

Untoward Effects and Poisoning.—When a large dose is taken, the symptoms of a therapeutic dose, dryness of the mouth and throat, thirst, and dysphagia, rapidly increase in intensity, the propulsion of blood by the arterioles into the capillaries assuming greater violence.* The cutaneous flush then becomes very marked; the congested brain and cord cause violent excitement, delirium, spasmodic choreiform movements of the face and extremities, and also convulsions, during which the patient may die.

When large toxic doses are taken, the sympathetic center is more violently irritated than the others, and hyperconstriction of the arterioles follows.* Those of the anterior pituitary and heart being contracted with the rest, inhibition of their functions occurs,* and collapse is brought on more or less suddenly. Intense muscular weakness which soon lapses into paralysis, particularly of the lower extremities, a rapid, then slow, weak and irregular pulse and heart-beat, shallow and irregular respirations, stupor and coma then follow in quick succession, the patient dying of respiratory failure.

Autopsies of cases in which death occurs during the period of intense vascular engorgement show this condition very clearly in all tissues, including the brain and cord. "At the autopsy of a subject poisoned by belladonna," writes Manquat,[illegible] "no characteristic lesion is found; the changes witnessed are limited to a considerable hyperæmia of the cerebro-spinal meninges and of the cortex, congestion of the parenchymatous organs and of the mucous membranes, dryness of the throat, and a few ulcerations or sphacelous areas of the stomach." Wood[illegible] says the post-mortem lesions are "congestion of the lungs and of the membranes, and even of the substance of the brain and cord," and refers to Lematre's[illegible] observation that "congestion of the retina is an almost characteristic lesion."

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* *Author's conclusion.*

[illegible] Manquat: *Loc. cit.*, p. 780, 1903.

The *treatment of belladonna and atropine poisoning* is described in a special section at the end of this volume.

Therapeutics.—The many therapeutic virtues that have been credited to belladonna are sustained by the foregoing analysis. Not only does it provide the blood with an excess of adrenoxidase, and, therefore, of auto-antitoxin, but it stimulates also the centers which augment the circulatory activity of the blood where its antitoxic properties can be productive of the best results.[*] In short, belladonna, owing to its alkaloid, atropine, produces an artificial fever.[*]

It is principally in disorders of the respiratory system that belladonna and its preparations are most efficaciaus. The various disorders due to *exposure to cold* and damp, are brought about by the sudden depression of catabolic activity[*] in the tissues, the trypsin, which plays the active rôle in the process, requiring the normal temperature of the body to break down waste products adequately. Cold, by inhibiting this process, causes the accumulation of imperfectly catabolized wastes in the blood and its consequences—*coryza, pharyngitis, tonsillitis*, or *bronchitis*, the location of the disorder corresponding usually with one which previously has been the seat of catarrhal congestion. Here, belladonna by increasing the antitoxic activity of the blood in all capillaries and raising the temperature therein. not only antagonizes directly the morbid effects of cold, but causes prompt destruction of all toxic wastes.[*]

In *bronchial asthma, neuralgia, migraine* and *hay-fever*, ascribed to the gouty "diathesis," which means the presence of alloxuric bases or intermediate waste products in the blood, belladonna is beneficial through a similar process.[*] In *asthma* due to hypotension of the arteries, it is also efficacious by increasing the blood's asset in adrenoxidase and causing thereby a rise of blood-pressure and more perfect oxygenation; thus meeting the two morbid factors of the disorder. Spasm, such as that of *rheumatic torticollis, dysmenorrhœa, enuresis* due to cystic irritability, etc., are also due to hypocatabolism in many instances, and atropine, by promoting the destruction of spasmogenic wastes, causes muscular relaxation.

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[*] *Author's conclusion.*

[illegible] Wood: *Loc. cit.*, thirteenth edition, p. 170, 1906.

[illegible] Lematre: Cited by Tardieu: "Etude médico-legale et clin. sur l'Empoisonnement," p. 752, Paris, 1867.

The reported beneficial effects from the use of atropine in infectious *erysipelas, scarlet fever, typhus,* etc., are doubtless due to the fact that it increases the antitoxic properties of the blood. Its tendency to cause dryness of the mouth and skin, however, is a contraindication to its use.

In asthenic disorders atropine is of great value. In *shock,* which is due mainly to paresis of the sympathetic center,* it is the best drug at our disposal; not only does it act directly upon the paretic center,* but it raises the blood-pressure and restores the capillary circulation of the heart and skin to its normal vigor*—provided alcohol is avoided. This applies as well to *collapse* in the asthenic stage of any disease, including the acute infections, especially when the heart is showing evidences of weakening. It is also one of the most effective remedies at our disposal for the relief of *night-sweats* in phthisis or the *colliquative sweats* that attend the advanced stages of many diseases. This symptom is likewise due to general vasodilation and to relaxation of the sudoriferous mechanism. Atropine not only tends to correct this condition, but also to counteract any toxæmia that may be present.*

DRUGS WHICH RESEMBLE BELLADONNA IN THEIR PHYSIOLOGICAL ACTION.

The physiological action of *homatropine hydrobromide, hyoscyamus, hyoscyamine sulphate* and *stramonium* is similar to that of belladonna, though their effects are less marked, their stimulating influence on the various centers mentioned being less violent.

DIGITALIS.

Physiological Action.—In therapeutic doses digitalis increases the nutrition of the heart and its functional power.

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* *Author's conclusion.*

This is due to the concurrent influence of three effects produced by the drug.* ***Two of these*** **are direct and energetic stimulation *of the test-organ and through it the adrenal center*, and also, but with less violence, *the sympathetic centers*, which enhances the propulsive action of the arterioles. As a result of the first action, the proportion of adrenoxidase in the blood is increased and general metabolism is enhanced throughout the body.* The muscular elements of the blood-vessels and of the cardiac muscle being influenced similarly,* their contractile power is increased, though the heart's action is slowed by the augmented resistance which the reduced caliber of the vessels entails.**

"In our experiments upon the exposed mammalian heart," writes H. C. Wood,[61] "we have seen in the final acts of digitalis drama happenings so curious and unexpected that at present no proposed theory as to the action of the drug is sufficient." This is mainly due to the belief that the drug acts directly upon the heart as it does experimentally. That it does not, however, is shown by the following facts: The weakest solution that will act on the isolated heart at all is that of 1 to 50,000. To produce any effect in an adult man supplied with but 13 pounds of blood, therefore, at least 1 grain (0.06 gm.) of digitalin would have to be given orally, since $^1/_4$ grain, "the full therapeutic dose" (Wood), would only make a solution of 1 to 200,000. The hypodermic use of the drug shows a still greater discrepancy, since Deucher[62] found that a dose of digitalis thus given produced the effects of a dose four times larger administered orally. A solution of digitalin in the blood-mass of 1 to 800,000 (equal to $^1/_{16}$ gr.—0.004 gm.) thus becomes active, though totally inadequate experimentally, *i.e.*, though sixteen times weaker than the weakest solution that will affect the isolated heart. And this allows nothing for the antitoxic action of the blood, which further reduces the strength of the drug, or for any dispersion in the lymph mass, which is twice greater than that of the blood. Nor does it allow for the fact that an isolated heart does not have to overcome the resistance of the blood-column which it must raise each time it contracts.

This is further emphasized by the fact that division of the adrenal and vasomotor nerve-paths from the pituitary annuls the effects of digitalis. Thus, transection of the *upper* part of the spinal cord was found by Bezold and Boehm[63] to cause a very marked fall of blood-pressure in an animal under the influence of digitalis, while Traube and Boehm and others[64] found "that after section of the cord high up the arterial pressure is either elevated not at all, or not nearly so much, by digitalis as in the normal animal." Wood (Sr. and Jr.) regard this as "a strong indication that the drug increases the arterial pressure largely by increasing the peripheral resistance without centric vasomotor stimulation." This points also to adrenals as the source of the vasoconstricting influence, for Langley[65] found, in a series of experiments with adrenal extract, that its action "runs parallel with the action of the sympathetic nerves on the blood-vessels," and that "in many cases the effects produced by the extract and by electrical stimulation of the sympathetic nerve correspond exactly." Now, as the peripheral arterioles are governed by the sympathetic, the adrenal secretion corresponds in its action with that of this nerve, because its action (as adrenoxidase) on the arterioles is the first to manifest itself, owing to their diminutive size. Now, digitalis, acting mainly *through the adrenal secretion*, also increases the peripheral resistance—but not by a direct action of the drug as is generally believed.

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* *Author's conclusion.*

[61] Wood: *Loc. cit.*, thirteenth edition, p. 318, 1906.

[62] Deucher: Deut. Archiv f. klin. Med., Bd. lviii, S. 47, 1897.

[63] Boehm: Archiv f. d. ges. Physiol., Bd. v, S. 153, 1872.

[64] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 319, 1906.

[65] Langley: Jour. of Physiol., vol. xxvii, p. 237, 1901.

The effects of digitalis on metabolism, in consequence of its action on the adrenal center, is well shown in the following lines by Manquat:[66] "The exchanges are increased, and oxidations augmented, and urea is excreted in greater abundance. According to von Broeck, the modifications of urea and carbon dioxide correspond with that of the blood-pressure: the elimination of urea and carbon dioxide increases as long as the pressure remains high; it diminishes when the blood-pressure recedes." The effect of therapeutic doses under these conditions suggests itself. "There occurs," says Cushny,[67] "an improved nutrition of the whole body," while after the use of digitalis and its allies in dilation of the heart, this organ "is found better nourished and has more of a tendency to hypertrophy." This applies also to the marked rise of blood-pressure. Thus, Wood[68] states that after a full dose of suprarenal capsules, "there is developed a slow, full pulse, followed very shortly by a great rise of the blood-pressure,"—precisely the action of digitalis.

The nutrition of the heart-muscle, along with that of all other structures, is aided materially by the slight (only when the average therapeutic dose is given) stimulating action which the drug has upon the sympathetic center, and therefore upon the blood-propelling activity of the arterioles.* Hence,* the fact that besides the rise of blood-pressure and the greater power of the contractions referred to above, the pulse-waves become larger, fuller and harder.

The action of the drug on the sympathetic center is illustrated by the concordance between the effects of direct stimulation of the pituitary body and those of digitalin on the blood-pressure. The only two centers in the pituitary which, on excitation, can produce such an effect are the adrenal center and the sympathetic center. That it is the latter is shown by the fact that the pressure begins to recede *at once* (reaching, in fact, below the normal within one minute) when the stimulation ceases—which would not occur if the adrenals were also stimulated, since the excess of secretion would not only cause a rise of pressure, but sustain it for a time. The similarity of the effects referred to are shown by the following comparative tables prepared by independent experimenters: Arnold and H. C. Wood, Jr.,[69] and Massay:[70]—

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* *Author's conclusion.*

[66] Manquat: *Loc. cit.*, vol. ii, p. 17, 1903.

[67] Cushny: *Loc. cit.*, fourth edition, p. 452, 1906.

[68] Wood: *Loc. cit.*, eleventh edition, p. 513, 1900.

[69] Arnold and H. C. Wood, Jr.: Amer. Jour. Med. Sci., Aug., 1900.

[70] Massay: Annales de la Soc. roy. des sci. méd. et natur. de Bruxelles, T. xii, p. 1 to 20, 1903.

DIGITALIN.
(*Arnold and H. C. Wood, Jr.*)

Dog: 9.5 kilograms.	PRESSURE.
Prior to injection.....	80 mm. Hg.
1 hour 10 min. after 0.02 gm.	104 " "
30 min. after injec. of 0.04 gm.	122 " "
After division of both vagi:—	
Dog: 8 kilograms.	
Prior to injection.....	167 mm. Hg.
50 min. after 0.04 gm.	200 " "
1 hours 40 min. after.	140 " "
4 hours 20 min. after.	240 " "

PITUITARY, EXCITATION OF.
(*Masay.*)

Dog: 2.6 kilograms.	PRESSURE.
Prior to excitation....	81 mm. Hg.
First excitation	144 " "
Second excitation	200 " "
After division of both vagi:—	
Dog: 5 kilograms.	
Prior to excitation....	162 mm. Hg.
First excitation	280 " "
After 15 seconds......	270 " "
Second excitation	252 " "

On the digitalin side the pressure is sustained, of course, because the stimulation of the adrenal and sympathetic centers persists until the blood rids itself of the poison. This accounts for a feature of the problem which so far has escaped notice, *viz.*, that the effects of digitalis are practically identical with those of suprarenal extract. Wood[71] describes (under separate headings) these effects in the following words:—

DIGITALIS.	SUPRARENAL EXTRACT.
"During the first stage there is marked slowing of the heart's beat, with large, full, hard pulse-waves and pronounced rise in the arterial pressure."	"When to an animal the full dose of suprarenal capsules is given there is developed a slow, full pulse, followed very shortly by a great rise of the blood-pressure."

The third effect of digitalis is also due to its stimulating action on the adrenal center.* The adrenal secretion being considerably increased, it enhances the contractile power of the right ventricle while in transit through it on its way to the lungs.* Hence the dicrotism and other phenomena which point to loss of parallelism between the action of the ventricles when large doses are administered.*

As to the third factor, *i.e.*, the direct action of the adrenal secretion on the right ventricle, we have seen,[72] that Brown-Séquard, over fifty years ago, emphasized the importance of the *venous* blood in cardiac dynamism, and that his belief that CO_2 was the active agent in the process caused his observations—all solidly established experimental facts—to be set aside. I pointed out, however, in the first volume that the effects observed were due to the presence of the adrenal secretion in the blood of the inferior vena cava, Oliver and Schäfer having shown that adrenal extract could cause marked contractions of the cardiac muscle. Digitalis being a powerful adrenal stimulant, it should normally increase the contractile power, *not* of the left ventricle, with which it does not come into contact, but *only* of the right—an important point in practice. Now, Germain Sée[73] has laid stress on the fact that digitalis acts mainly on the right ventricle. Openchowski,[74] who had also found, in 1889, that the action of digitalis was greatest on the right side of the heart, recently noted diminution of the activity of the left ventricle—a true functional dissociation. Cushny likewise[75] states that digitalis, strophanthin and helleborein all "increase the output of the right ventricle."

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* *Author's conclusion.*

[71] Wood: *Loc. cit.*, eleventh edition, pp. 297, 513, 1900.

[72] *Cf.* this vol., p. 807.

[73] Germain Sée: Sajous's "Annual and Analyt. Cyclo.," vol. ii, p. 526, 1888.

[74] Openchowski: Berl. klin. Woch., Bd. xli, S. 1045, 1904.

The kidneys being subjected to all the conditions which digitalis awakens in other organs, their functional activity is enhanced by doses sufficiently large to increase the propelling power of the arterioles and the intrinsic metabolism of their functional elements.* Hence the *diuresis* produced by digitalis.* Conversely, when the dose is excessive, the renal arterioles become so constricted that functional inhibition, *i.e.*, *anuria*, occurs.

The first action is self-explanatory in view of the evidence adduced above. As to the constrictor effects, Lauder Brunton[76] writes: "Digitalis contracts the arterioles of the kidney sooner than those in other parts of the body. The renal vessels may contract so much as to arrest the secretion of urine altogether, although the general blood-pressure is high."

Untoward Effects and Poisoning.—Digitalis, especially when administered during a prolonged period and in small doses, may cause a variety of untoward phenomena. In some cases, these are mainly due to what has been termed "*cumulative action*"—which, from my viewpoint, means hypersensitiveness of the sympathetic center, a condition due to the persistent excitation to which the drug submits it. At first the sympathetic center is overstimulated and undue propulsive activity of the arterioles* causes headache, hallucinations and delirium, dryness of the throat through crowding of the lumina of the acini, dilation of the pupil, abdominal cramps, digestive disorders, pains in the limbs recalling those of rheumatism. These symptoms may be accompanied by disturbance of the cardiac rhythm, dicrotism, etc., due to excessive stimulation of the right ventricle.* After a time, however, the sensitiveness of the sympathetic center being greater than that of its fellow,* its own phenomena take the lead:* hyperconstriction of the arterioles is produced, and signs of collapse may appear, including weakness and irregularity of the cardiac action, due to impending arrest of cardiac functions, the case culminating perhaps as one of acute poisoning.

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* *Author's conclusion.*

[75] Cushny: *Loc. cit.*, fourth edition, p. 448, 1906.

[76] Lauder Brunton: Trans. of the 13th Inter. Med. Congr., Sect. on Therap., p. 263, 1900.

In acute poisoning, the patient passes through the stage of hyperæmia—which may include violent headache, flushing, muscular pains, vomiting, delirium, etc.—more or less rapidly, then into the stage of depression, just referred to. The heart action becomes irregular, and on exertion, such as sitting up or rising, extremely weak; the ventricles and auricles may no longer beat synchronously; the two ventricles likewise, or portions of the myocardium, may dilate, while others still contract. Hence the irregular action, the occasionally observed blowing systolic murmur, the dicrotic, rapid, weak, irregular and broken pulse. The vascular pressure suddenly drops, concomitantly with general relaxation of the entire muscular system, as shown by the intense muscular prostration, the anuria—due, in part, to inaction of the bladder—the lowered reflex activity (François-Franck[77]) and the widely dilated pupil. Paroxysms of suffocation occur, the adrenal secretion and its carrier, the venous blood of the inferior vena cava, being no longer propelled to the pulmonary alveoli by the cardiac muscle.[*] Hence[*] the steady fall of temperature, the cold extremities, the growing pallor and the stupor.

A symptom of another order may appear in this connection towards the end of this stage: the gradual diminution of the blood's antitoxic attributes preventing the adequate conversion of toxic wastes into benign and eliminable products,[*] convulsions appear. A recurrence of very elevated blood-pressure then occurs, followed by a very rapid fall and death.

That the arterioles play the cardinal rôle in these morbid phenomena has been observed by various investigators. Wood[78] refers to the experiments of Fothergill,[79] Gourvat and Ackermann,[80] who found microscopically that "the *arterioles* of the frog's web or of the mesentery of the rabbit undergo very marked contraction, even to the *obliteration of their lumen*, after the exhibition of digitalis." Weil[81] also noted that the reflex activity of the spinal cord practically disappeared when large doses were given. The drug caused such intense vasoconstriction that the central and peripheral circulations were impeded, and the nervous elements, deprived of blood, lost their irritability. Porter,[82] after an exhaustive physiological study of the *cumulative* action of digitalis, found that it was the result of excessive contraction of the heart's artertoles and of the consequent arrest of the nutrition of the myocardium. Suggestive in this connection is the fact that transection of the upper part of the cord by Traube, Besold and Boehm (a procedure which, we have seen, arrests the effects of digitalis) at once restored normal conditions in poisoned animals—obviously by causing relaxation of the arteries. This result could not have occurred if the vasoconstriction had, as is now believed, been due, even in part, to a direct action of the drug upon the vascular walls.

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[*] *Author's conclusion.*

[77] François-Franck: Sajous's "Annual and Analyt. Cyclo.," vol. ii, p. 526, 1898.

[78] Wood: *Loc. cit.*, thirteenth edition, p. 318, 1906.

[79] Fothergill: "Digitalis, Its Mode of Action and Use," Phila., 1871.

[80] Gourvat, Ackermann: Berl. klin. Woch., Bd. ix, S. 27, 1872.

[81] Weil: Archiv f. Anat. u. Physiol., S. 262, 1871.

[82] Porter: American Medicine, Apr. 27, 1901.

A fatal issue occurs rarely, according to Potain,[83] death from digitalis being most frequently met with in subjects suffering from Bright's disease, a rheumatic diathesis, anæmia or delirium tremens. Hence the need of special watchfulness in such cases. The prevailing opinion at present is that the dangers of digitalis have been greatly exaggerated. Henry Beates, Jr.,[84] who uses digitaline (Merck's Germanic) in relatively large doses, and obtains excellent results, is of this opinion.

The *treatment of digitalis poisoning* is described in a special section at the end of this volume.

Therapeutics.—The foregoing interpretation of the physiological action of digitalis accounts fully for its beneficial action in certain cardiac disorders. Thus, in *uncomplicated dilation,* in which the heart-muscle fails to contract adequately, a condition usually occurring as a result of general adynamia, digitalis, or better digitalin, not only enhances markedly the nutrition of the body at large, but that of the heart in particular, increasing greatly its dynamic power. In *dilation due to a valvular lesion,* mitral in most cases, and due to the increased resistance of the blood-column, digitalin is of great value to aid the heart in overcoming the obstruction. Even when the *valves of both sides* are diseased the drug is of value; here the passive resistance to the admission of blood to the right heart causes hyperæmia and venous stasis, and the excess of adrenal secretion causing a rise of blood-pressure, more blood is projected towards the heart, and slows cardiac action, thus giving the organ more time to dilate and to admit more blood.

Conversely, the use of any preparation of digitalis is obviously *inadmissible* when the heart has reached the stage of full compensation, *i.e.*, hypertrophy; when a cardiac disorder is due to, or accompanies, arteriosclerosis, in cases of aortic regurgitation, since the drug would in the latter case, by slowing the cardiac action, lengthen the diastole and afford more time for regurgitation. Moreover, by causing general vasoconstriction, it would increase the resistance to the blood-current and help to detain the blood in the ventricle.

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[83] Potain: Jour. de méd. et de chir., vol. lxxi, p. 248, 1900.
[84] Henry Beates, Jr.: Monthly Cyclo. of Pract. Med., Jan., 1905.

In *syncope* and *collapse* of asthenic origin, digitalin is of very great value, since it influences very soon, when administered hypodermically, the centers and organs which underlie the whole vital fabric. In *neurasthenia*, its action on general nutrition, besides that on the heart, renders it invaluable in some cases. In acute adynamic diseases, especially *pneumonia*, it aids powerfully to sustain the heart. It is not indicated during the stage of early pulmonary engorgement, however, since it augments the vascular tension. When the heart is yielding to the resistance of the blood-column, it is far better to relieve the pressure itself by means of the bromides or veratrum viride.

STROPHANTHUS.

Physiological Action.—Like digitalis, strophanthus increases the power of the cardiac contractions and reduces their frequency. The pulse-waves become larger and fuller and the blood-pressure is raised when sufficiently large doses are administered. This action is less marked, but it occurs sooner than under the influence of digitalis, and does not last as long.

Strophanthus likewise owes its action to the fact that it stimulates actively the test-organ, and through it the adrenal center.* A greater quantity of adrenal secretion being produced, the contractile power of the right ventricle is enhanced.* The increased volume of the adrenal secretion insuring a corresponding augmentation of adrenoxidase in the blood, the metabolic activity of all organs is raised.* As this includes the heart-muscle, the latter is also better nourished and its contractile power is thus increased from another direction.*

This applies as well to the arteries. Their walls being supplied with blood richer than usual in adrenoxidase, their tonic activity is raised, and when the dose of the drug is sufficiently large they contract.* As is the case under the influence of digitalis, the arterioles are the first vessels (owing to their diminutive lumen) to show evidences of constriction.* An important difference between strophanthus and digitalis asserts itself in this connection, however, *viz.*, strophanthus does not excite the sympathetic center even when administered in large doses.* Hence the fact that, although almost as active as an adrenal stimulant as digitalis,* strophanthus does not influence the arterioles as energetically as does the former.

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* *Author's conclusion.*

Cushny[55] states that "in the pulmonary circulation, the pressure is not raised by some of the [digitalis] series, such as strophanthin and helleborein, while after digitalis a very distinct rise in the pressure in the pulmonary artery is sometimes seen. Yet," he adds, "*all* of them increase the output of the *right* ventricle." He characterizes these phenomena a "paradox," but their cause is self-evident when we take into account the fact that it is this ventricle alone which receives the surplus of contractile impetus afforded by the adrenal secretion.

The fact that strophanthus does not excite the sympathetic center as does digitalis, is shown plainly by its relatively feeble action on the arterioles. Fraser[56] estimated that it was fifty times less active in this particular than digitalis. Balfour[57] states that, although its action is very much more marked on the heart than digitalis, it acts "one hundred times less powerfully than digitalis on the muscles of the arterioles." Pisani[58] also found clinically that strophanthus acted but slightly upon the vasomotor system, though he observed increased arterial pressure and reduction in the pulse-rate from 5 to 20 beats per minute. Fraser, Delsaux and Yeo[59] observed but little change in the caliber of the blood-vessels. The arterial contraction does not even become very marked under the influence of large doses. Popper, and Gottlieb and Magnus[60] found that division of the cervical cord or of the splanchnic does not prevent the rise of pressure, but these procedures, by causing relaxation of the arteries in the adrenals, increase the functional activity of the latter and cause a rise of pressure even apart from the drug. Günther,[61] after studying the action of the drug upon various kinds of animals, great and small, reached the conclusion that although strophanthus was a vasoconstrictor, this action "was not marked in overdosage."

Strophanthus also provokes diuresis, but less actively than digitalis, owing to the fact that the absence of all influence on the sympathetic center deprives it of any action on the propelling power of the arterioles.* The kidneys are merely stimulated, therefore, because they are rendered hyperæmic with blood unusually stimulating in character, owing to the excess of adrenoxidase it contains.*

The presence of hyperæmia is made evident by the fact that Drasche[62] and other observers found the secreting structures congested and hæmorrhagic in experimental animals after moderate doses of strophanthus.

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* *Author's conclusion.*

[55] Cushny: *Loc. cit.*, fourth edition, p. 448, 1906.

[56] Fraser: Jour. of Anat. and Physiol., vol. vii, p. 141, 1872; and Brit. Med. Jour., Nov. 14, 1885.

[57] Balfour: Lancet, May 23, 1896.

[58] Pisani: Gaz. med. di Torina, No. 32, 1899.

[59] Cited by Wilcox: Amer. Jour. Med. Sci., May, 1897.

[60] Gottlieb and Magnus: Archiv f. exp. Path. u. Pharm., Bd. xlvii, S. 135, 1901; Bd. xlviii, S. 262, 1902.

[61] Günther: Therap. Monatshefte, Bd. xviii, S. 285, 1904.

[62] Drasche: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 235, 1906.

Untoward Effects and Poisoning.—Large doses, or small doses given during a prolonged period, may produce nausea, vomiting, diarrhœa and marked diuresis, the heart's action and pulse being greatly slowed and strengthened. Muscular twitchings and abnormal reflex irritability may also occur. The heart muscle being likewise rendered overactive, and therefore oversensitive, it is prone, like the other muscles, to excessive activity, *i.e.*, contraction, and its diastoles become increasingly smaller; it finally fails to dilate at all, being found contracted after death. A general arrest of the vital functions follows at once: the temperature and the blood-pressure fall rapidly, muscular weakness lapses into paralysis, and death follows.

Fürbringer[53] and Hochhaus, out of 120 cases in which they used the drug, also observed three cases of sudden and unexpected death in which the drug had been used "in large doses and throughout a rather long time" As in every instance no post-mortem lesions capable of accounting for the untoward result were found, the authors ascribe them to the drug. Mayeur,[54] Lemoine[55] and others have noted cumulative effects resulting in death in some instances after giving small doses of strophanthus during a prolonged period. If we were dealing with cardiac paralysis incident upon excessive vasoconstriction, as in digitalis poisoning, the heart would be found dilated, *i.e.*, in diastole; but such is not the case. Fraser, Paul Bert, Gley[56] and others have found experimentally that strophanthin arrested the heart in systole. Other investigators have noted that it could arrest the heart in diastole, but this was obtained by applying the drug directly to the isolated heart—a procedure which, as we have seen, does not portray the behavior of drugs in the system. The sudden arrest of function this entails is exemplified by Wood's[57] reference to the experiments of Gley,[58] that "after poisonous doses the pressure immediately or secondarily falls gradually to zero."

The *treatment of strophanthus poisoning* is described in a special section at the end of this volume.

Therapeutics.—Strophanthus is indicated in the same conditions as digitalis. Unfortunately, it cannot be used hypodermically, owing to its marked irritating action on the tissues. Its oral use is of advantage to replace digitalis for a time, though less effective and more ephemeral in its action. As it does not affect the sympathetic center,* it will usually be borne without trouble by patients who cannot use digitalis.

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* *Author's conclusion.*

[53] Fürbringer: Deut. Medizinal-Zeitung, Jan. 23, 1888.

[54] Mayeur: Thèse de Lille, 1888.

[55] Lemoine: C. r. de la Soc. de biol., 8 série, vol. v, pp. 495, 533, 1888.

[56] Gley: Semaine médicale, vol. ix, p. 424, 1889.

[57] Wood: *Loc. cit.*, thirteenth edition, p. 236, 1906.

[58] Gley: *Loc. cit.*

DRUGS WHICH RESEMBLE STROPHANTHUS IN THEIR PHYSIOLOGICAL ACTION.

The physiological action of *apocynum* and *convallaria* is similar to that of strophanthus, the rise of blood-pressure provoked being also due to the increased metabolic activity in the vascular and cardiac muscles.* *Sparteine* stimulates the same centers as digitalis, but with less vigor as to the adrenal center.* The action on the sympathetic constrictors becomes paramount sooner, with the resulting hyperconstriction of the cardiac arterioles and depression.*

STRYCHNINE.

Physiological Action.—A prominent feature of the action of strychnine is that it stimulates the test-organ, and, therefore, the adrenal center.* By thus increasing the volume of adrenoxidase in the blood, it enhances oxygenation, and thereby the activity of the metabolic processes of the entire organism.*

Wood and Cerna[99] obtained experimentally concordant results in dogs, showing that "the injection of strychnine produces an extraordinary increase in the respiratory air-movement, the increase varying from 75 to 300 per cent." Identical effects were obtained in morphinized and chloralized animals. This is sustained by Reichert's[100] observations that the increase in heat production caused by the drug was a constant factor, favorable to an increase of temperature. Kionka[101] found that the drug caused a marked elevation of temperature, and Mosso[102] observed that this occurred even in a curarized dog. All this is confirmed by the fact ascertained by Obermeier,[103] that the production of carbon dioxide was greatly increased. It is evident, therefore, that strychnine powerfully enhances oxygenation.

The central origin of these phenomena was demonstrated experimentally by Stricker and Rokitansky.[104] Both these investigators concluded that strychnine was a stimulant of the respiratory centers. The identity of this center is suggestive by the fact shown by Schiff in 1850, Claude Bernard and others, that strychnine gives rise to glycosuria. Langendorff[105] having found lactic (sarcolactic) acid in the urine, it was believed that glycosuria was due to excessive catabolism due to the convulsions provoked by the drug, but Demant[106] showed that small doses, totally incapable of causing spasm, also caused glycosuria. Langendorff reached the same conclusion after experiments in frogs. Now, we have seen, that as observed by Loeb, Lorand, Caselli, Launois and Roy and others, lesions which stimulated the pituitary body gave rise to the symptom, and that it was produced by increasing the activity of the oxidation processes, *i.e.*, the production of adrenoxidase, through excitation of the adrenals. Indeed, we have seen that Blum, Herter and others caused glycosuria by injections of adrenal extract, and that Bernard prevented toxic glycosuria by dividing the splanchnic nerves, which contain the secretory nerves of the adrenals. It is by stimulating the adrenal center, therefore, that strychnine increases general oxidation. Stewart and Rogoff[106a] have confirmed this action experimentally.

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* *Author's conclusion.*

[99] Wood and Cerna: Jour. of Physiol., vol. xiii, p. 870, 1892.

[100] Reichert: Therap. Gaz., Mar. 15 to June 15, 1892.

[101] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 218, 1906.

[102] Mosso: Arch. ital. de Biol., vol. vii, pp. 306, 340, 1886.

[103] Obermeier: Inaug. Diss., Erlangen, 1891.

[104] Cited by Manquat: *Loc. cit.*, vol. ii, p. 700, 1903.

[105] Langendorff: Archiv f. Physiol., Suppl. Band., S. 269, 1886.

[106] Demant: Zeit. f. Chemie, 1886.

Strychnine also stimulates directly the bulbar vasomotor center.

That strychnine stimulates the vasomotor center is recognized by all experimenters. Referring to the experiments of Richter,[107] S. Mayer[108] and Vulpian, Manquat[109] states that it causes "a considerable elevation of the arterial pressure, which may attain the double of the normal level." Reichert[110] was also led to conclude by a large number of experiments, that the drug raised the blood-pressure by an action on the vasomotor center, but he found also, as had Vulpian, Mayer and Klapp,[111] that after division of the upper portion of the spinal cord (the path also of the adrenal secretory nerves), strychnine could no longer raise the arterial pressure.

Small therapeutic doses of strychnine, by thus increasing the oxygenizing property of the blood and simultaneously the vascular tone, enhance general metabolism and nutrition in all organs.* When the therapeutic doses are large, however, undue engorgement of the capillary system occurs,* and is manifested mainly by slight stiffness of the muscles, restlessness, formication and other cutaneous sensations, the other senses becoming also more acute.

Large therapeutic doses evoke the typical effects of the drug, *i.e.*, twitchings and "startings," provoked by slight excitations of the surface, beginning usually with the muscles of the jaw, throat, neck and chest and extending to other muscles. This culminates into tetanic convulsions when toxic doses are taken; but in the genesis of these convulsions a new factor asserts itself, *i.e.*, a marked exaltation of reflex activity due to the highly oxygenized condition of the blood* and the raised vascular tension. The morbid process is as follows:—

The general vasoconstriction caused by strychnine begins in the great central vascular trunks and affects only vessels supplied with a muscular coat,* excepting the arterioles (governed by the unaffected sympathetic center), which yield to the centrifugal pressure of the blood-stream.* The capillaries not being supplied with such a coat, the passively dilated arterioles thus become engorged with the blood forced into them by these deeper vessels and are dilated.* This general capillary congestion (with highly-oxygenized blood) increases, as stated, the functional activity of all organs;* but prominent among these are (1) the cutaneous sensory end-organs whose sensibility to external excitation is exalted; (2) the spinal cord, whose sensibility to afferent impulses is also enhanced; (3) the skeletal muscles, which are rendered overexcitable to impulses received from the spinal cord.*

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* *Author's conclusion.*

[106a] Stewart and Rogoff: Jour. of Pharmacol. and Exper. Therap. xiii. pp. 95, 167 and 242, 1919.

[107] Richter: Zeit. f. ration. Med., Bd. xviii, 1863.

[108] S. Mayer: Jahrb. d. k. k. Gesellschaft d. Aerzte zu Wien, S. 112, 1872.

[109] Manquat: *Loc. cit.*, vol. ii, p. 690, 1903.

[110] Reichert: *Loc. cit.*

[111] Klapp: Jour. Nerv. and Mental Dis., Oct., 1878.

Hence, the convulsion produced by strychnine is a reflex phenomenon due to the interaction of three sets of organs, and is produced in the following manner: the morbidly sensitive (hyperoxygenized) sensory end-organs of the skin send unusually violent afferent impulses to the (hyperoxygenized) overexcitable spinal cord, and this organ in turn sends exceptionally energetic stimuli to the overexcitable (hyperoxygenized) muscles.*

Alluding to the action of strychnine on the vasomotor system and the manner in which the vessels are influenced, Cushny[112] states that "the constriction seems to affect mainly the internal vessels, while those of the skin and perhaps of the muscles are dilated, and the blood-current is, therefore, deflected largely from the internal organs to the skin and limbs." Dastre and Morat and Wertheimer[113] found that strychnine produced such an energetic dilation of the peripheral vessels in doses of 0.002 to 0.004 gms. ($^1/_{30}$ to $^1/_{16}$ grain) that it caused a marked blush of the mucous membranes of the lips, gums and tongue. Delézenne[114] also noted that strychnine was a powerful dilator of the peripheral vessels—a fact accounted for by the absence of a muscular layer in capillaries; for, as Manquat[115] says, it is the vessels supplied with a "contractile tunic" which are constricted by the drug, since these are the only ones which are supplied with vasomotor nerves. Indeed Wertheimer observed that the peripheral dilation was most manifest after the blood-pressure had attained its maximum and disappeared together with the fall of pressure. The gravitation of blood towards the periphery is also emphasized by the clinical facts mentioned by Manquat, that "strychnine causes a painful exaltation of the sensibility of the organs of special sense, especially those of sight and hearing," and that "in medium doses (0.005 to 0.01 gm.—$^1/_{12}$ to $1^1/_2$ grains) tactile sensibility is augmented."

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* *Author's conclusion.*

[112] Cushny: *Loc. cit.*, fourth edition, p. 202, 1906.

[113] Wertheimer: Semaine Méd., vol xii, p. 345, 1892.

[114] Delézenne: Arch. de phys'ol norm et path., 5 série, vol. vi, p. 899, 1894.

[115] Manquat: *Loc. cit.*, vol. ii, p. 699, 1903.

The rôle of the cutaneous sensory organs in the genesis of convulsions is illustrated by the experiment of Poulsson,[116] who found that when a frog was poisoned with strychnine the convulsions did not occur after the animal had been dipped in a solution of cocaine. Obviously, as stated by Cushny in reference to this experiment, the cocaine used "was sufficient to paralyze the sensory terminations." Moreover, we know that a draught of air, the slightest touch or a loud noise is sufficient to provoke a convulsion in strychnine poisoning.

That the spinal cord is the source of the spasmogenic impulses is well known. But is its overactivity due, as generally believed, to direct irritation by the strychnine, or to local hyperæmia with overoxygenized blood? Various irritants applied to the bulbar cord, *i.e.*, physical irritants (Magendie), can provoke convulsions. As shown by Van Deen,[117] Valentin and Spence,[118] strychnine will diffuse itself in the blood of the brain and cord when placed on these organs, and provoke convulsions from muscle to muscle as it advances in the cord. Yet this does not prove that a dose, when ingested or injected, quite able to provoke convulsions, will act in the same way; it only shows that strychnine is, as elsewhere, a local irritant. Cushny,[119] in fact, adduces evidence which led him to conclude that tetanus "can be produced in parts whose motor cells are unpoisoned." Again, Brown-Séquard and Martin-Magron and Buisson divided the cord below the fore-legs, and isolated the lower or detached segment of the cord from the circulation by dividing its blood-vessels. On injecting strychnine convulsions occurred only in the portion of the body connected with the upper, *i.e.*, normal, segment of the cord. Nor does this prove that it was because the vessels could no longer carry strychnine to the spinal cells of the lower segment that convulsions did not occur in the lower portion of the body, since destruction of the vessels prevented the hyperæmia of the source of the spasmogenic impulses, the corresponding area of the cord. Such a condition evidently exists in strychnine poisoning, for Wood refers to "indications of spinal hyperæmia" observed at times *post-mortem*, while Cushny[120] states that the local cellular changes seem "to indicate hyperactivity of the cell, which need not necessarily be due to direct action of the poison on it."

The rôle of the adrenoxidase in the cord is exemplified in experimental results recently recorded by Burdon-Sanderson and Buchanan.[121] These investigators (in refutation of views advanced by Baglioni) showed that "when the cord of a strychnized preparation is alternately cooled and warmed by a stream of cold or warm water, the rest of the body being protected as far as possible from the influences of the changes of temperature, the frequency of the responses *varies* according to the *temperature* to which the cord is exposed." As we have seen,[122] the rôle of the adrenoxidase in the organism is to combine with the nucleo-proteid in order to liberate heat energy and thus enhance metabolism. The presence of an excess of adrenoxidase in the blood of the cord by raising metabolism in the cell-elements does, therefore, what immersion in warm water produced in Burdon-Sanderson and Buchanan's experiments, *i.e.*, it increases its activity as the source of the stimuli transmitted to the muscles. That such an excess of adrenoxidase, and therefore a large reserve of oxygen, obtains is also shown by the fact that Meltzer and

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[116] Poulsson: Archiv f. exp. Path. u. Pharm., Bd. xxvi, S. 22, 1889.

[117] Van Deen: Physiol. de la Moëlle épinière, iii, 120, 1860.

[118] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 215, 1906.

[119] Cushny: *Loc. cit.*, fourth edition, p. 199, 1906.

[120] Cushny: *Loc. cit.*, fourth edition, p. 200, 1906.

[121] Burdon-Sanderson and Buchanan: Jour. of Physiol., vol. xxviii, No. 5, p. xxix, 1902.

[122] *Cf.* this vol., p. 895 *et seq.*

Salant[123] kept an animal poisoned with strychnine alive thirty minutes, and free from cyanosis, dyspnœa or asphyxia, by insufflating pure hydrogen. This gas delayed death by interfering with the intake of oxygen and reducing the excess of vascular tension, the animal living all the while on the large volume of oxygen in his blood. Moreover, Evenhof[124] observed that an injection of strychnine enabled the patient to bear greater quantities of chloroform—another fact which the presence of a greater quantity of oxygen in the blood explains.

Vulpian[125] long ago concluded that "all spasmodic phenomena caused by strychnine are reflex in nature." Claude Bernard[126] cut all the posterior roots of the spinal nerves, in the frog. Having injected strychnine, convulsions occurred *only* when the segments of the nerves connected with the cord were stimulated. Obviously the cord required this exogenous excitation to produce spasm. According to Wood,[127] this experiment "demonstrates that the reflex motor ganglionic cells are incapable of originating an impulse, and in strychnine-poisoning are simply in such a *condition of overexcitability* as renders them exceedingly sensitive to slight irritations and causes them to respond most energetically to the feeblest stimulus, the convulsions always being therefore a reflex phenomenon." Cushny[128] also concludes that convulsions "follow only on the passage of an impulse *from without* to the spinal cord." Finally, that the convulsions are due to impulses from the cord to the muscles is shown by a simple experiment of Vulpian's, *i.e.*, division of the nerves to any one extremity. This procedure prevents strychnic spasm in that extremity, though all other muscles take part in the convulsion.

Poisoning.—A poisonous dose of strychnine evokes with more or less rapidity the symptoms caused by a large therapeutic dose: stiffness of the face, neck and chest; involuntary twitches; heightened reflex irritability; hypersensitiveness of the special senses, etc. More or less suddenly—sometimes within a quarter of an hour after taking the dose—the convulsions begin, the patient falling with the legs rigidly extended, the body being so bent backward as to rest upon the head and heels (opisthotonos). The facial muscles are strongly contracted, the corners of the mouth being drawn out—the so-called *risus sardonicus*. All the morbid processes described are clearly discernible in this sequence of phenomena. The paroxysm finally lapses into tremor and intermittent muscular contractions, then ceases, leaving the subject in a state of intense exhaustion and calm. The slightest external excitation, a current of air even, suffices to bring on another paroxysm similar to the first, and this may be followed by a third.

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[123] Meltzer and Salant: Jour. of Exp. Med., vol. vi, p. 107, 1902.
[124] Evenhof: Russky Vratch, June 18, 1905.
[125] Vulpian: "Leçons sur l'action physiol., etc.," Paris, 1882.
[126] Claude Bernard: "Leçons sur les effets des substances toxiques et méd.," Paris, 1857.
[127] Wood: *Loc. cit.*, thirteenth edition, p. 216, 1906.
[128] Cushny: *Loc. cit.*, fourth edition, p. 198, 1906.

In man, a favorable termination is probable when the convulsions gradually become less intense and shorter, while the intervals become longer. Conversely, in unfavorable cases, the paroxysms become more intense until the vasoconstriction is such as to interrupt the circulation, as shown by the cyanosis of the lips and face. This interruption of the circulation is the main lethal factor, for it not only interferes with functions of the adrenals, but so reduces the *vis a tergo* motion of the blood-current that the venous blood laden with adrenal secretion is not driven past the pulmonary alveoli with sufficient speed to form the minimum quantity of adrenoxidase required by the vital process at large.* The normal issue under such conditions is death from asphyxia—that observed in strychnine poisoning.

The steady increase of the vascular tension which ultimately leads to the fatal issue is well shown by the observations of Santesson,[129] that the action of strychnine on the terminal ramifications of the nerves in the frog increases slowly and progressively with the dose until a maximum is reached. Finally there comes a time when their action is paralyzed. Vulpian and Poulsson[130] also observed this paralyzing action of strychnine on motor nerves. This is readily explained, however, by the intense vasoconstriction caused by the drug, for inasmuch as motor nerves incite functional activity merely, as we have seen,[131] by acting as stricto-dilators, *i.e.*, by admitting a greater volume of blood in an organ, complete obstruction of the channels containing that blood must render the motor nerves useless, *i.e.*, paralyze their action.* Indeed, after injecting a large toxic dose into the jugular of a dog, "the motor nerves," as stated by Wood, were found "to have entirely lost their power of responding to galvanic or other stimulation." Further proof that this is merely due to excessive contraction of the arteries is afforded by the fact that it may be, as shown by Vulpian, only temporary, the motor nerves regaining the functional efficiency even before the effects of the drug have passed off.

The inhibition of the adrenal functions is a normal consequence of the excessive constriction. The pituitary body and the heart, receiving finally a volume of blood quite inadequate to sustain their functions, can no longer continue its functions.

Therapeutics.—The foregoing study of the action of strychnine justifies the great confidence it has earned. In *functional atony,* the increase of adrenoxidase and the simultaneous stimulation of the vasomotor center provide not only the vital principle, but also the mechanism to increase the supply of this substance to the enfeebled organs.* In the various forms of *paralysis*, *neurasthenia*, etc., an important feature of its action imposes itself, viz., the increased circulation of adrenoxidase-laden plasma *in* the nervous elements themselves, axis-cylinders, the network of the cell-bodies, the dendrites,* etc., in addition to that supplied to the nerves through their nutrient arteries. In *cardiac disorders*, attended with local debility and vascular relaxation, strychnine, by stimulating the adrenal center, increasing metabolic activity in the muscular layer of the vessels and in the heart-muscle proper,* affords precisely the conditions required to counteract the asthenic process. In *alcoholism*, strychnine, by enhancing the production of adrenoxidase, antagonizes precisely its evil effects,* since, as will be shown, it is by robbing the blood of its oxygen that alcohol produces its main toxic action.* In *amblyopia* due to alcoholism, the marked benefit strychnine affords is due to a similar action. In *shock*, a condition mainly due to paretic vasodilation, it strikes directly the depressed center,* increases oxygenation of the vascular walls* and restores the vascular tone to its normal state. Finally, in *chronic bronchitis* and other torpid processes, strychnine is of great value by increasing the oxygenizing power of the blood,* and stimulating thereby all the reparative functions.*

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* *Author's conclusion.*

[129] Santesson: Archiv f. exper. Pathol. u. Pharm., Bd. xxxv, S. 57, 1895.

[130] Poulsson: *Loc. cit.*

[131] *Cf.* this vol., p. 1115 *et seq.*

DRUGS WHICH RESEMBLE STRYCHNINE IN THEIR PHYSIOLOGICAL ACTION.

The physiological action of *brucine* differs in no way from that of strychnine. It is less active as a spasmogenic agent, and less reliable.

Caffeine acts much as does strychnine. It activates the adrenal center with even more vigor, however, thus increasing markedly the proportion of adrenoxidase in the blood.* Although its action on the vasomotor center is less marked, it is sufficient to raise the tone of the vessels and heart, the nutrition of these organs being materially aided by the increased oxygenizing property acquired by the blood under its use.* Its indications are practically those of strychnine. Its marked action on the vascular system and the heart has also caused it to be used as a substitute for digitalis.

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* *Author's conclusion.*

COCA AND COCAINE.

Physiological Action.—Cocaine owes its therapeutic properties to the fact that it stimulates (1) the test-organ and through it the adrenal center,* and (2) the vasomotor center. Its action on the adrenal center is very powerful, the adrenal secretion and its product adrenoxidase being increased in the blood even by small doses, while general metabolism is augmented in proportion as the therapeutic dose is increased.* This is the characteristic action of nontoxic doses of cocaine.*

Cocaine is more powerful as an adrenal stimulant than either belladonna, digitalis or strychnine. E. T. Reichert[132] refers to it as "a thermogenic of extraordinary power." He found[133] that in dogs "general metabolism is distinctly increased even by small doses, and that the extent of the increase is proportional to the size of the dose." In two series of experiments, for instance, the heat-production was increased 40 per cent. by a dose of 0.0025 gm. per kilo of body weight, and 146.9 per cent. by one of 0.01 gm. per kilo, the mean temperature rise in the first series being 0.55° C. (1° F.) and 1.81° C. (3.26° F.). With still larger doses the rectal temperature rose beyond this (2.19° C.—4.94° F.) before the experiment ceased. Indeed, Wood[134] states that "the rise of rectal temperature in cocaine-poisoning sometimes amounts to as much as 8° F." (4.44° C.), and moreover that the drug "is a powerful stimulant to the respiratory centers"—a conclusion based on the investigations of von Anrep, Mosso and others. That the adrenal center—the respiratory center—is the source of the impulses which provoke these effects is shown by the fact pointed out by von Anrep, Berthold[135] and Reichert,[136] that preliminary division of the upper portion of the spinal cord prevents all the effects of cocaine. By increasing the secretion of the adrenals its action on the heart may become sufficient to arrest it in systole—the characteristic final effect of cocaine on this organ, according to Pachon and Moulinier.[137]

Similar effects are obtained from the coca plaint itself. Gazeau found that coca leaves taken daily increased the respiratory activity, the temperature, and the excretion of urea: 18 gm. (4 1/2 drachms) taken daily increased the output of urea 11 per cent., and 20 gm. (5 drachms), 16 per cent. The latter dose accelerated the pulse and the respiratory rate. These observations were confirmed by Espinosa. Mantegazza had previously observed an increase of temperature. Gazeau, Morton,[138] Haig[139] and Mortimer,[140] all assert that it frees the blood of products of tissue-waste—a property due, as is well known, to increased oxidizing power.

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* *Author's conclusion.*

[132] Reichert: Therap. Gazette, July 15, 1902.

[133] Reichert: Univ. Med. Mag., May, 1889.

[134] Wood: *Loc. cit.*, thirteenth edition, p. 204, 1906.

[135] Berthold: Centralbl. f. med. Wissen., Bd. xxiii, S. 435, 1885.

[136] Reichert: Amer. Lancet, May, 1891.

[137] Pachon and Moulinier: C. r. de la Soc. de biol., 10 série, vol. v, p. 566, 1898.

[138] Morton: Jour. of Nerv. and Mental Dis., Oct., 1879.

[139] Haig: "Uric Acid as a Factor in the Causation of Disease," London, 1897.

[140] Mortimer: "Peru, History of Coca," p. 425, New York, 1901.

The direct action of cocaine upon the vasomotor center is much less pronounced than that of strychnine.* Though it raises markedly the blood-pressure, this is mainly due to the fact that its powerful stimulating influence upon the adrenal center and the general increase of metabolic activity this entails, affect likewise the heart-muscle and muscular elements of the blood-vessels, arteries and veins.* The volume of blood driven into the capillaries of all organs is therefore increased (by the contraction of the larger vessels), but not excessively, as it is by drugs which excite violently the vasomotor center.* The increase of volume, however, plus the marked gain of oxygenizing power acquired by the blood, represent the immediate effects to which coca and cocaine owe their therapeutic action.*

That cocaine raises the blood-pressure has been shown by von Anrep,[141] Vulpian,[142] Laborde, Nikolsky, Danini, Reichert[143] and others. The fact that the arterioles take part in the general constriction is indicated by the observation of Durduß[144] that the narrowing of the arteries of a rabbit's ear, which occurs after cocaine has been ingested into this animal's blood, is prevented if the cervical sympathetic of the corresponding side is severed. According to Mortimer,[145] coca, given internally, also "contracts the peripheral arteries." That all these effects are originally of central origin is shown by the fact that when the adrenal and vasomotor paths are severed, they cease. Thus, Danini, Berthold[146] and Reichert found that after section of the spinal cord alone or with the vagi, cocaine no longer distinctly increases the blood-pressure.

The crowding of the highly oxygenized blood into the peripheral tissues causes the effects of cocaine to resemble those of belladonna. Thus, Cushny[147] states that "the pulse is accelerated, the respiration is quick and deep, the pupil generally dilated," and that "headache and dryness of the throat are often complained of." The fugacious preliminary slowing of the heart's action, also observed under atropine, was noted by both Vulpian and Arloing, while dilation of the pupil has been noted by Koller, Terrier,[148] Laborde,[149] von Anrep and others. It occurs also fifteen to twenty minutes after a solution of cocaine has been applied. Cocaine also, as stated by Manquat, causes a slight paresis of accommodation and increases pain in glaucoma, thus showing that it increases intra-ocular tension—as does atropine.

The effects of the coca plant are evidently similar. Shuttleworth[150] noted that it caused dryness of the throat; Mantegazza[151] and Gazeau[152] both observed acceleration of the pulse. Mortimer[153] says that "after mastication of a *great* quantity of coca, the eye seems unable to bear light," and that "there is marked distention of the pupil," referring to the observations of Tschudi,[154] Schroff[155] and others.

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* *Author's conclusion.*

[141] von Anrep: Archiv f. d. ges. Physiol., Bd. xxi, S. 38, 1880.

[142] Vulpian: C. r. de l'Acad. d. sci., Nov. 24, 1884.

[143] Reichert: Amer. Lancet, May, 1891.

[144] Durduß: Deut. med. Woch., Bd. xiii, S. 172, 1887.

[145] Mortimer: *Loc. cit.*, p. 412.

[146] Berthold: *Loc. cit.*

[147] Cushny: *Loc. cit.*, fourth edition, p. 299, 1906.

[148] Terrier: Bull. de la Soc. de chir., vol. x, p. 825, 1884.

[149] Laborde: Tribune méd., Nov. 30, 1884.

[150] Shuttleworth: Can. Pharm. Jour., Aug., 1877.

[151] Mantegazza: "Sulle virtu della Coca," Milan, 1859.

[152] Gazeau: Thèse de Paris, 1870.

It is owing to its powerful stimulating action upon the adrenal center and its less marked, though effective, action on the vasomotor center, that coca and cocaine owe their energetic excito-motor properties.* The volume of blood supplied to the tissues is not only greater, but, its oxygenizing virtues being unusually high, the intrinsic metabolism of all cellular elements is correspondingly enhanced.* It is through this property that coca activates the nutrition of all muscles.* The muscle fiber is also enriched in those substances which serve to cause its contraction, since the surplus of adrenoxidase in the blood likewise augments the functional activity of the liver and of the leucocytogenic organs.* The carbohydrate reserves (the most important of which is glycogen) are thus supplied to the muscles in greater quantities (though commensurate with the supply of adrenoxidase), and the potential energy which the increased nutrition supplies can thus be converted into a correspondingly greater amount of muscular work.*

Mosso found that in warm-blooded animals, including man, muscular excitability was increased by small doses. Fuster, in experiments upon himself, experienced marked muscular agitation and tremors, with impulses to physical movements. Benedicenti[156] also found ergographically that cocaine raised not only the contractile energy of the muscles, but also their power to resist fatigue. Ott showed that the contractions were prolonged. The convulsions caused by toxic doses occur, as observed by Grasset,[157] five or six minutes after the drug has been injected, and may be brought on by peripheral excitation, thus showing, in accord with the conclusions of Mosso, von Anrep, and Soulier and Guinard,[158] that the reflex activity of the spinal axis is markedly increased. This is not due, as generally believed, to a local action of the drug, but to the excess of adrenoxidase in the plasma of the nerve-cells.*

The leaves of the coca plant have been extensively used by the natives of Peru, Bolivia and other South American countries, to increase their muscular strength and endurance. According to various medical authors, Tschudy,[159] Unamié,[160] Moreno y Maíz[161] and others, who witnessed its use in these countries, the plant undoubtedly possesses this property. Sir R. Christison[162] observed experimentally upon himself that it removed extreme fatigue and prevented it, suspending also hunger and thirst. Reichert[163] also found that under restricted diet, and even in the absence of food, coca enables its user to do more work than under normal conditions.

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* *Author's conclusion.*

[153] Mortimer: *Loc. cit.*, p. 413.

[154] Tschudi: Reiseskissen aus Peru, S. 42, 1838.

[155] Schroff: Wochenbl. d. k. k. Ges. d. Aerzte zu Wien, 1862.

[156] Benedicenti: Untersuchungen zur Naturlehre des Menschen u. d. Thiere. Moleschott, Bd. xvi, S. 170.

[157] Grasset: C. r. de l'Acad. des sci., Feb. 9, 1885.

[158] Soulier and Guinard: Lyon méd., vol. lxxxviii, p. 465, 1898.

[159] Tschudy: *Loc. cit.*

[160] Unamié: "Dict. d'Histoire nat.," Paris, 1803.

[161] Moreno y Maiz: Thèse de Paris, 1868.

Mortimer[164] concludes that the increased muscular power is caused by coca "through the excitation of the hypothetical ferment of the contractile element." That such an action prevails—though indirectly—is evident from the facts I have submitted. Indeed, the function of adrenoxidase is dual here, as it is in all tissues: it takes part in the intrinsic metabolism of the muscular protoplasm as it does in that of all cells, a function which, in its catabolic phase, utilizes the ferment or hydrolytic triad.[165] This is the trophic element of the process, however—that through which the life of the muscle-cell is sustained as well during repose as during contractile activity. This does not mean that coca or cocaine supplies nutriment to the muscle, but that it augments its functional activity by raising its power to utilize the nutrient materials that are available.

The anæsthesia produced by the local application of cocaine is due, as is well known, to a marked vasoconstrictor action. The tissues, including their sensory terminals, being deprived of blood, lose their sensibility. This property of cocaine differs entirely from that of the same agent when it is used internally—the only action which enters within the scope of this work.

Untoward Effects and Poisoning.—An excessive dose of *coca* produces mental excitement and an exacerbation of muscular power, but this is apt to be followed by general weakness, especially of the legs, cutaneous horripilation, coldness and difficult locomotion. These are obviously the after-effects of excessive intrinsic muscular metabolism.

Cocaine, in toxic doses—which include small as well as large doses—gives rise to symptoms due in practically all cases to excessive excitation of the adrenal center. This is aggravated, however, by a concomitant rise of the blood-pressure through supranormal metabolism in the muscular layers of the blood-vessels, a corresponding overaction of the cardiac muscle from the same cause and excitation of the sympathetic center. As a result, blood excessively rich in adrenoxidase is forcibly driven into all organs. The following phenomena are produced: the cerebral hyperæmia provokes marked excitement and hallucinations, the patient being very talkative, wakeful, and perhaps anxious and confused. The pulse is accelerated, the respiration rapid, the mouth and throat dry, and the pupils dilated. Gradually as the general vasoconstriction increases these symptoms become more marked, and profuse perspiration, creeping sensations in the skin, convulsive movements and præcordial distress appear; the cardiac action becomes extremely rapid and irregular, the respiratory movements likewise, dyspnœa becoming steadily more marked. If the toxic dose be not too large, these phenomena may gradually disappear, leaving the patient extremely weak, especially in the lower extremities. Otherwise violent tonic and clonic convulsions appear, and death occurs in the midst of a paroxysm. In such cases the heart is found tightly contracted. Its diastoles become more and more restricted, and the volume of blood raised is gradually lessened until finally it ceases to dilate. This mode of death is due to excessive stimulation of the adrenal center and to paralysis of the heart by excessive contraction of its ventricles.*

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[162] Sir R. Christison: Brit. Med. Jour., Apr. 29, 1876.
[163] Reichert: Univ. Med. Mag., Oct., 1890.
[164] Mortimer: *Loc. cit.*, p. 420.
[165] *Cf.* this vol., p. 851.

In some cases, especially when the toxic dose is very large, the convulsive stage does not appear; the patient, after a few of the preliminary symptoms, lapses into a state of profound collapse, the pulse being weak, small and intermittent, and sometimes slow. The heart here, though still active, is unable, owing to the cramped condition of its walls, to dilate sufficiently, and, too little venous blood being sent to the lungs during each contraction, respiratory failure occurs.* The respirations become increasingly slow and shallow; the skin grows cold, clammy and cyanotic, and death follows, but due in this case to respiratory paralysis.

Death from cocaine-poisoning is evidently not due to inhibition of the heart. Pachon and Moulinier[186] found the ventricles tightly contracted and the auricles dilated. That a relatively small dose may produce such effects is well shown by the following case reported by Tivy[187]—one of urethral stricture with retention of urine. He states: "I resolved to get a small catheter or bougie into his bladder if possible, and, to save the patient some of the pain and so facilitate the process, I decided to inject some solution of cocaine into the urethra beforehand. I therefore injected half a drachm of a 10-per-cent. solution of cocaine hydrochloride with a glass syringe into the urethra in the ordinary way, telling the patient to hold the penis in his fingers to prevent escape. I then left the patient with the wardsman who was attending me, and turned to wash my hands; but before I could get to the end of the ward the man called to me, and I returned immediately. I then found the patient in a state of clonic convulsion, with his back arched, and jumping up off the bed. His jaws were moving spasmodically, and he had bitten his tongue. His face was somewhat cyanosed and his breathing very spasmodic and slightly stertorous. The eyeballs were fixed and the lids half closed. I could not feel a pulse at the wrist, but his arms were jerking so forcibly that it was not easy in any case. I put my ear to the chest and heard the heart beating. His breathing rapidly became shallower and convulsions lessened in force, and in about a minute respiration ceased, the cyanosis increasing; I put in a gag, pulled out his tongue, and began artificial respiration, and the Sister brought me a hypodermic syringe of brandy, which she injected while I continued the respiration. I also had a hot stupe put over the heart, but when I listened again the beats had ceased. I persevered with artificial respiration for a quarter of an hour and had the brandy repeated, but with no effect, as the patient never rallied, and was, I believe, dead in about three minutes from the time of injection. I made a post-mortem examination the next day and found all the organs fairly healthy. The kidneys were congested but not diseased, the spleen was enlarged and fleshy, and the liver showed signs of cirrhosis. The heart had apparently stopped in systole, as all the chambers were empty." The participation of the entire muscular system in the morbid process and the influence on the heart are clearly shown.

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* *Author's conclusion.*

[186] Pachon and Moulinier: *Loc. cit.*

[187] Tivy: Brit. Med. Jour., Oct. 6, 1906.

The second mode of death is really but a slight modification of the first. The "cramped" heart, instead of stopping outright, continues its functions in an imperfect manner; it necessarily fails to satisfy the needs of the respiratory process, and the function, as a whole, sooner or later comes to a standstill. A suggestive fact in this connection is the observation of Dujardin-Beaumetz[128] that doses no larger than 0.01 or 0.02 gm. ($^1/_6$ to $^1/_3$ grain) never caused syncope in his cases when the patient was either standing or sitting. In the recumbent position the heart's tendency to become arrested in systole, *i.e.*, in the cramped state, is increased, since the upright position, by augmenting the intra-ventricular resistance of the blood-column, tends to prevent contraction of the ventricles.

Chronic Cocainism.—The stimulating action of cocaine upon the adrenal and sympathetic centers is attended, when any but very small doses penetrate the blood-stream, by an unusual expenditure of local latent energy, followed by a period of depression and recuperation. Gradually, as the doses are repeated, the recuperative power of the centers decreases and the depression experienced not only persists, but tends to lapse into prostration, especially in neurotic subjects. Soon the discovery is made that this prostration, which entails apathy, apprehension, inability to do satisfactory work, etc., is at once antagonized by the drug itself. Strength, agility, self-confidence, etc., return, but continue only as long as the effects of the drug last. Stimulated, the adrenals have temporarily enriched the blood's supply of oxidizing substance; stimulated, the sympathetic centers caused the enriched blood to be driven vigorously into the tissues and the entire nervous system. Yet the centers, having sacrificed a correspondingly great amount of their energy, become increasingly less responsive to the exciting influence of the drug, and gradually, as the prostration augments after each exacerbation of activity, the dose must be increased in order to insure satisfactory effects. Finally the patient shows evidences of rapidly-developing marasmus—the result of the general vasodilation and the deficiency of adrenoxidase which the debility of the adrenal center entails. The skin assumes a pale yellowish color, the extremities are cold; digestive disorders, due to relaxation of the gastro-intestinal muscular elements and deficiency of digestive ferments, appear, with anorexia and emaciation as normal sequences. The sympathetic center also losing its hold upon the arterioles, there occur hallucinations of vision, hearing, taste, smell and cutaneous sensibility—the patient imagining that foreign bodies, creeping bugs, etc., are present in his skin—insomnia, delirium and delusions of persecution, sometimes attended with furor, during which the patient may injure himself or others, convulsions, general paralysis and insanity.

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[128] Dujardin-Beaumetz: Manquat: *Loc. cit.*, vol ii, p. 399, 1903.

The experiments of Reichert[169] in dogs clearly illustrate another fact, *i.e.*, the depression which the active effects of cocaine produce: the 0.0025 gm. dose (per kilo weight) increased the temperature 0.55° C., but caused no subsequent depression; the 0.01 dose raised it 1.81° C., but it became *subnormal* during the third hour; in the two succeeding experiments with still larger doses the temperature, after a marked rise, also became subnormal and continued so throughout the experiment. In man, as stated by Norman Kerr:[170] "When the dose taken has been relatively immoderate, the depression and nervous debility may remain for days or till the next dose."

The *treatment of cocaine poisoning* is described in a special section at the end of this volume.

Therapeutics.—Apart from its local action (a feature of its use, which does not enter within the limits of this work) cocaine is of great value in all disorders in which *general adynamia* prevails. Unfortunately, the vigor with which it overcomes the symptoms, *i.e.*, by stimulating the adrenal center, whose debility underlies the morbid process,* is so gratifying to the patient, if adequate doses are taken, that he is exposed to the danger of indulging inordinately in its use, *i.e.*, acquiring the cocaine habit. To avoid this, small doses or, better still, preparations of the coca plant should be prescribed, the aim being to raise *gradually* the functional efficiency of the adrenal center to its normal standard. This measure avoids also the depression which follows the use of large doses.

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* *Author's conclusion.*

[169] Reichert: *Loc. cit.*

[170] Norman Kerr: Sajous's "Annual and Analytical Cyclo.," vol. ii, p. 312, 1898.

I have not given cocaine itself internally since the first two years of its appearance on the market, over twenty years ago; two experiences having shown me its dangers. I use a preparation of uniform strength, the Mariani coca wine, which contains $^1/_{10}$ grain (0.006 gm.) of cocaine to the ounce (as one of the constituents of the coca leaf), and prescribe it in the regular way, avoiding the word "cocaine" (Vinum Erythroxylon C. Mariani), and directing that it be put up in an ordinary pharmaceutical bottle. While ordering one ounce to be taken three times daily, however, I give simultaneously digitalin ($^1/_{10}$ grain—0.006 gm.), or strychnine ($^1/_{60}$ grain—0.001 gm.), and lay stress on the importance of the last-named drugs. The patient's attention is thus diverted from the cocaine, and experience has shown that he is not exposed to the danger of becoming a cocainomaniac. Mariani wine has of late contained no cocaine, however, and the uncertain U. S. P. wine of coca is alone available.

Coca and cocaine have been found of especial value in *neurasthenia, debility* and *retarded convalescence,* owing to its effects on general metabolism not only upon the muscular tissues, but also the nervous elements proper.[*] This accounts also for their value in all forms of *paralysis* dependent upon general asthenia, and in *melancholia* due to cerebral ischæmia. In *cardiac disorders* in which functional atony and dilation prevail, they serve much the same purpose as digitalis, strophanthus and kindred drugs.[*] Their beneficial effects are especially marked in the weak heart of delayed convalescence from debilitating diseases, influenza, for example. This applies also to *torpid catarrhal processes* and *particularly* to *chronic bronchitis,* the increased vigor of cardiac contractions and the greater oxygenizing power of the blood serving to increase the circulatory activity in the bronchial mucosa[*] and to incite and hasten resolution. In disorders of the gouty series, *migraine, asthma,* etc., they tend to prevent the recurrence of accesses by increasing the oxygenizing and antitoxic properties of the blood and,[*] therefore, its power to break down the toxic products[*] of imperfect metabolism, while simultaneously, by activating the metabolic process itself, preventing the formation of toxic wastes.[*] They also afford material aid in the asthenic stage of infectious diseases, *typhoid fever, yellow fever* and *smallpox* especially, by increasing the blood's asset in auto-antitoxin* and by sustaining the contractile power of the heart. Coca is one of the most efficient agents at our disposal in the treatment of *alcoholism;* by stimulating directly the test-organ, and through it the adrenal center,* it counteracts the debilitating action of alcohol on this center and the craving for alcoholic stimulation.

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[*] *Author's conclusion.*

QUININE.

Physiological Action.—Moderate doses of quinine stimulate the general vasomotor center and cause general vasoconstriction. Contraction of the central vascular trunks being thus produced, the blood supplied the peripheral vessels is increased,* and the reflex sensibility of the cutaneous sensory nerves is correspondingly influenced.

"Quinine," says Manquat, "always causes, in the state of the vessels, modifications related to those of the pressure. Weak doses give rise to vasoconstriction and large doses to a vasodilation." This was conclusively demonstrated experimentally by H. A. Hare,[271] who observed that in frogs under the influence of quinine, the vessels were much more contracted (their walls being also thicker) than those of normal frogs. Von Schroff,[272] in accord with this observation, had found that quinine caused a preliminary rise of blood-pressure, an effect also noted experimentally by Schlockow,[273] Block, Neissner,[274] Jerusalimsky,[275] Sée and Bochefontaine[276] and others. It is further confirmed by the fact that the peripheral congestion caused by the constriction of the central vascular trunks becomes sufficiently marked to greatly increase the sensibility of the cutaneous nerve-endings. This was first observed by Schlockow, who found that quinine increased the skin's reflex activity. Heubach[277] and Cerna[278] reached similar results experimentally, but found that this was produced only by very small doses; they also conclude that since it was prevented by ligation of the abdominal aorta, it was to be ascribed to overactivity of the peripheral sensory nerves.

This indicates that the general vasoconstriction is of central origin, for, as we have seen, convulsions are caused in frogs by excessive stimulation (*i.e.*, hyperæmia) of the cutaneous sense-organs, such as that produced by quinine and other alkaloids of cinchona. Albertoni[279] found that the convulsions thus produced by cinchonidin in pigeons occurred, even though the cerebrum had been removed, provided the drug were injected after the animal had been given time to recover from the shock of the operation. This shows that the indirect cause of the convulsions originated not in the cortex, but in structures below the brain. Indeed, they occurred also in dogs after destruction of the cortex. Moreover, Jerusalimsky found that the rise of blood-pressure caused by quinine did not occur after transection of the spinal cord, which, of course, contains the vasomotor paths.

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* *Author's conclusion.*

[271] Hare: Phila. Med. Times, Oct. 18, 1884.

[272] von Schroff: Med. Jahrb., S. 175, 1875.

[273] Schlockow: "De Chinii Sulfurici, etc.," Vratislaviæ, 1860.

[274] Block, Neissner: Nothnagel et Rossbach: "Mat. méd. et thérap.," French edition, p. 635, Paris, 1889.

[275] Jerusalimsky: Centralbl. f. med. Wissen., Bd. xiv, S. 476, 1876.

[276] Sée and Bochefontaine: C. r. de l'Acad. de sci., vol. xcvi, p. 267, 1883.

[277] Heubach: Centralbl. f. med. Wissen., Bd. xii, S. 674, 1874.

[278] Cerna: Phila. Med. Times, July 3, 1889.

[279] Albertoni: Arch. f. exper. Path. u. Pharm., Bd. xv, p. 278, 1882.

Larger therapeutic doses likewise stimulate the general vasomotor center, but this action is soon supplemented by another, *i.e.*, direct stimulation of the *sympathetic* center, and, as a result, by increased propulsive activity of the terminal arterioles.[*] The peripheral vessels are thus not only supplied with an unusual volume of blood, but the pressure to which the terminal arterioles submit the latter as it passes through them forces the blood into the cutaneous capillaries with sufficient violence, generally, to cause marked flushing.[*] A sensation of fullness in the head and ears, due to cerebral hyperæmia, may be accompanied by more or less severe headache, tinnitus and deafness, the latter being sometimes permanent, especially when the use of the drug is continued.

Occasionally hæmaturia, purpura, erythema and subdermal swelling appear, the latter phenomenon being due to the fact that the blood or its serum is forced through the walls of the capillaries, owing to the centrifugal pressure exerted upon them by the blood-stream.[*]

The cardiac action is accelerated and strengthened under these conditions, the heart-muscle receiving a greater influx of blood.

The intense hyperæmia of the capillaries is well shown by the investigations of St. John Roosa[180] and Kirchner,[181] the first-named investigator having found that in adequate doses the drug caused congestion of the middle ear. Kirchner not only confirmed this observation, but found that it produced, in cats, hæmorrhages in the middle and internal ears and in the fourth ventricle. The latter phenomenon shows that the aural symptoms are due to a *general* excessive engorgement of the capillary system, the blood, as in hæmaturia and the cutaneous vascular lesions, causing often actual rupture of the vessels. This is illustrated by the familiar fact that quinine often provokes epistaxis, with considerable relief, sometimes, of the severe headache caused by the drug.

Quinine is poisonous to many organisms, including amœboid cells. So marked is this action that adequate doses check the amœboid movements of the leucocytes themselves and prevent their migration from the vessels. The tissues failing to receive their usual proportion of nucleo-proteid granules,[*] nutrition is lowered. Hence[*] the decreased elimination of urea caused by excessive doses of the drug.

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[*] *Author's conclusion.*

[180] St. John Roosa: Amer. Jour. Med. Sci., Oct., 1874.

[181] Kirchner: Berl. klin. Woch., Bd. xviii, p. 725, 1881.

It is to its direct action as a toxic upon the plasmodium malariæ that quinine produces its beneficial effects in the various malarial fevers. It destroys not only the amœba, but its spores, and thereby breaks up the morbid cycle. The activity of this process is enhanced by the stimulating action of the drug upon the vasomotor center; the blood being driven in greater quantities into the capillary system and the liver, a fever-like process is awakened, in which the drug acts as the immunizing agent.[*] The volume of blood in transit through the capillaries is sufficiently increased in some instances to produce a rise of temperature reaching sometimes 105° F. (40.6° C.). In such cases the adrenal center is also stimulated by the drug.[*]

The toxic action of quinine upon the leucocytes was first shown by Binz[182] in 1867. So marked was its action in this particular that areas of inflammation in the mesentery of frogs produced by the local application of mustard failed to be invaded by leucocytes when quinine had been given to the animal, while they were present in great number in the untreated animals. This has been confirmed by Maurel,[183] Pouchet[184] and others. Fitch[185] found that in animals poisoned with quinine the polymorphonuclear leucocytes are considerably reduced in number. These leucocytes are the neutrophiles—those which, as I have shown,[186] take up the food-products from the intestine. The result of this destruction of leucocytes, which necessarily diminishes the supply of granulations to the tissue-cells and metabolism is self-evident: deficient nutrition of the entire organism. That quinine produces, in fact, a marked diminution of urea excretion has been noted by many observers. Referring to this evidence, and particularly to Prior's,[187] Wood, Sr. and Jr.,[188] write, "we are warranted in believing it established that quinine powerfully depresses the elimination of the nitrogenous excretory principles."

The direct action of the drug on the plasmodium is generally recognized. As to the febrile process sometimes awakened by quinine, cases have been reported in which the temperature rose several degrees. Thus, A. L. Goodman[189] refers to a case in which the drug raised the temperature from 99° to 103.2° F., twice, the temperature receding when the drug was withdrawn, and he refers to many reported cases, including nineteen by Prof. Tomasselli, of Catania, in some of which the temperature reached 105° F. (40.6° C.).

Luca,[190] in a study of the relative value of the administration of the drug by the mouth or by hypodermic injection, ascertained that the quantity in the blood is at first very minute, but that it increases gradually, the maximum being reached in an hour. This is doubtless due to the fact that, as held by Lombard and Carles,[191] leucocytes ingest quinine and are poisoned by it. The alkaloid then passes out into the blood again or is promptly secreted by these cells. Luca found also that the parasite of malaria was susceptible to a minute proportion of the drug.

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[*] *Author's conclusion.*

[182] Binz: Archiv f. micros. Anat., Bd. iii, S. 383, 1867.

[183] Maurel: Rev. inter. de Bibliogr., Sept. 25, 1892; Arch. de méd. expér. et d'anat. path., vol. xv, p. 37, 1903.

[184] Pouchet: "Leçons de Pharmacodynamie," p. 250, 1902.

[185] Fitch: Yale Med. Jour., June, 1905.

[186] *Cf.* this vol., p. 1027.

[187] Prior: Archiv f. d. ges. Physiol., Bd. xxxiv, S. 237, 1884.

[188] Wood, Sr. and Jr.: *Loc. cit.*, thirteenth edition, p. 570, 1906.

[189] Goodman: Med. Rec., Dec. 1, 1906.

[190] Luca: Archives Ital. de Biol., Mar., 1905.

Untoward Effects and Poisoning.—In subjects unduly susceptible to its effects, owing to hypersensitiveness of the sympathetic center,* very small doses of quinine have caused untoward effects. Under normal conditions, even moderate doses (15 to 30 grains—1 to 2 grams), by unduly stimulating the sympathetic center,* become harmful. They provoke such powerful contraction of the arterioles that the penetration of blood into the capillary system is interfered with.* As a result, the peripheral hyperæmia caused by the smaller doses is replaced by anæmia of the cutaneous capillaries.* This naturally entails lowering of the temperature of the surface; hence the antipyretic effects of the drug, when administered in large doses.

The arterioles of the various structures of the eye being likewise excessively constricted,* the quantity of blood supplied to them is correspondingly diminished. The vision may thus become impaired, or total blindness may occur, sometimes quite suddenly. Quinine amblyopia usually disappears gradually, however, after the use of the drug is discontinued. The light reflex is usually absent and accommodation may also become impossible. Nystagmus, strabismus and anæsthesia of the conjunctiva have also been observed. The pupils are dilated when the constriction of arterioles* of the sphincter muscles of the iris is sufficiently marked.

The corresponding constriction of the terminal arterioles* in various other organs also interferes with their functions: the cerebral (capillary) anæmia gives rise to vertigo; that of the spinal system and the skeletal muscles to marked muscular weakness and a tremor resembling that of paralysis agitans; that of the lungs and in the body at large to marked dyspnœa; that of the myocardium to slowing and weakening of the heart's action. Collapse may then occur, death being sometimes preceded by convulsions. Such an issue, however, is extremely rare.

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* *Author's conclusion.*

[191] Carles: "Rôle des Leucocytes," p. 94, Paris, 1904.

All these morbid effects are aggravated, when very large doses are taken, by the destruction of leucocytes which such doses provoke.

The transition from hyperæmia to anæmia of the cutaneous capillaries is well illustrated by the fact that in frogs very small doses produce, as stated by Wood,[102] "a permanent palsy of reflex activity." The cause of this has remained obscure. This may be said also of the antipyretic action of quinine. "While no solution of this dilemma has been offered as yet," says Cushny,[103] "it seems extremely probable that the antipyretic action of quinine is due to its retarding metabolism." He characterizes as a "paradox" also the fact that while "on the one hand, there is no question that the temperature falls," "the combustion is certainly not reduced to any notable extent." Another unexplained fact is that noted by de Mussy in 1871, and more recently by Huchard,[104] that large doses of quinine arrest hæmorrhage. All these effects are readily explained when excessive (sympathetic) constriction of the terminal arterioles is taken into account: the palsy of reflex activity is due to the reduced volume of blood in the capillaries; the temperature falls for the same reason, though combustions are not materially reduced; hæmorrhages are controlled because the constricted vessels no longer allow the blood to pass freely, and thus favor the formation of obturating clots.

The constriction of the ocular arterioles under the influence of large doses was directly observed by De Bono[105] in dogs. The vessels of both the iris and choroid were markedly contracted in most instances—those of the optic nerves always. He found the "quinine-amblyopia ischemia" in the retina of all cases, whether cured or not. As stated by Wood,[106] "the ophthalmoscopic examination commonly, but not always, has revealed pallor of the optic disks, with excessive lessening in the size of the retinal vessels." The exceptions are, obviously, those in which the doses were not large enough to provoke ischæmia. Indeed, smaller doses may induce the opposite effect—the hyperæmia to which I have referred. Thus, Dickinson "has seen the optic disks swollen and having the appearance of an ordinary choked disk." The presence of quinine ischæmia is further emphasized by the fact that de Schweinitz found that "the continuous administration of the drug may finally cause a true atrophy of the optic nerve"—a normal result of inhibited nutrition. Both Brunner[107] and de Schweinitz[108] ascribe the loss of retinal function to a vasomotor spasm probably of centric origin, but such a spasm would mean the presence of general vasoconstriction, a condition which would entail engorgement and not depletion of the peripheral vessels. Again, vasomotor spasm does not exist under such conditions. "When the doses of quinine are large (1.5 to 2 gms. [23 to 30 grains])," write Nothnagel and Rossbach, "whether in man or animals, during disease or health, the contractions of the heart and the vascular pressure is *lowered;* most observers (Briquet, Duméril, Reil, Schlockow, Lewitzky, Schroff, Jr., Liebermeister) consider this as an indubitable and constant fact." Indeed, we are dealing, not with vasomotor spasm, but with spasm due to excitation of the *sympathetic* center, the terminal arterioles of the eye being throttled, as it were, as are those of the body at large.

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[102] Wood: *Loc. cit.*, thirteenth edition, p. 562, 1906.
[103] Cushny: *Loc. cit.*, third edition, p. 565, 1899.
[104] Huchard: Jour. des Praticiens, Dec. 8, 1900.
[105] De Bono: Arch. d. Ottal., vol. ii, fasc. 3 to 6, 1895.
[106] Wood: *Loc. cit.*, thirteenth edition, p. 562, 1906.
[107] Brunner: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 562, 1906.
[108] de Schweinitz: *Ibid.*

The *treatment of quinine poisoning* is described in a special section at the end of this volume.

Therapeutics.—The use of quinine as an antipyretic is now obsolete, other remedies and measures being preferable when hyperpyrexia (above 105° F.) is to be reduced to prevent hæmolysis. Its tendency to produce destruction of the red and white corpuscles in large doses also argues against its employment in the febrile diseases. In *all forms of malarial fever*, and conditions due to malaria, *neuralgia, enlargement of the spleen*, etc., however, quinine is invaluable, its power exceeding that of any other remedy. It is customary to precede its use by a mercurial purgative: the powerful stimulating action of mercury upon the test-organ and adrenal center[100] accounts for the increased effect thus obtained.* On the other hand, the production of *malarial hæmaturia*, sometimes witnessed when quinine is given in intermittent fevers, is explained by the intense capillary hyperæmia to which the drug gives rise,* and points to the need of moderation in its use. As a *prophylactic* against malarial infection, quinine is now of recognized value. This property is due to the cutaneous hyperæmia which the drug produces* and to the fact that the parasite or its spores, when introduced into the tissues by the mosquito, at once meet blood which is toxic to them, owing to the presence of quinine in solution.

It is also by producing capillary hyperæmia, especially of the cutaneous tissues,* that quinine is beneficial in many other conditions. It can thus* abort *acute coryza, tonsillitis, subacute bronchitis*, etc., if taken early and in sufficient quantities: 3 grains (0.2 gram) every two hours until slight headache or flushing of the face occur, when the dose is reduced.* The toxic wastes liberated in the blood through exposure to cold are thus promptly destroyed* where they have accumulated, *i.e.*, in the superficial tissues.* Suppurative processes, *boils*, for instance, are promptly arrested by this treatment. In asthenic disorders, *neurasthenia*, quinine is of value by causing the nerve-elements, which are in reality all capillary blood-channels,* to receive a greater volume of blood-plasma.*

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* *Author's conclusion.*

[100] *Cf.* this vol., p. 1167.

DRUGS WHICH RESEMBLE QUININE IN THEIR PHYSIOLOGICAL ACTION.

A number of drugs act much as does quinine, the variations consisting in their action upon the different centers. Thus *eucalyptus* stimulates the adrenal, vasomotor and sympathetics centers, but mainly the latter. Indeed, when toxic doses are given, death is due to excessive constriction of the arterioles of the heart and failure of the respiration. Eucalyptus is much less effective than quinine, or, in fact, any preparation of cinchona, as antiperiodic.

DRUGS WHICH BECOME CONSTITUENTS OF THE TISSUE-CELLS.

Closely associated with the drugs described in the foregoing pages is the class of agents generally known as "nutrients," in the sense that they are actual components of the tissues. They are of great value, therefore, as adjuncts to these drugs in appropriate cases, since the latter only stimulate function without contributing directly to the body's resources.

Iron owes its therapeutic value to several concomitant properties. Being a normal constituent of tissue and blood-cells, its beneficial effects appear only when it is actually required. It stimulates the adrenal center only incidentally—probably before it has assumed an assimilable form. Its specific action, however, is to take part in the elaboration of hæmatin, of which it is the chief component, and to stimulate the bone-marrow—thus increasing the production of red corpuscles. Its purpose in hæmatin being, as I have shown, to act as storage material (the link being its own affinity for oxygen) for adrenoxidase, pending the distribution of the latter to the tissues, iron thus enhances directly the blood's all-important function, oxygenation.

In *phosphorus* we have another constituent of tissue-cells even more widespread than iron, and fully as important to the vital process. The various rôles I have ascribed to it in all organic functions, *e.g.*, in the maintenance of the blood's temperature, in the body's auto-protective processes, in the intrinsic exchanges of the tissue-cells, including the nerve-cells, and the genesis of the nerve-impulse, etc., emphasize sufficiently its therapeutic indication in adynamic disorders, especially those in which the nervous system has borne the brunt of the original pathogenic factor. Being, like iron, a component of the tissues, it affects the nerve-centers morbidly only when given in toxic doses. In therapeutic doses, especially when it forms part of an organic compound, phosphorus is building material, and is essentially beneficial as such when given with such agents as digitalis, coca, strychnine, etc., which activate metabolism and the mechanism of nutrition, without, however, as stated above, contributing directly to the body's assets.

IRON.

Physiological Action.—Iron being an important constituent of the blood and tissues, its effects become manifest only when the quantity available in the body is inadequate to satisfy the needs of the functions in which it takes part.* The earliest beneficial influence obtained is an increase of general oxygenation, and, therefore, of general metabolic activity. This is due to an incidental stimulation of the test-organ and adrenal center by the iron carried thereto by the leucocytes.* As iron is likewise an active stimulant of the hæmatopoietic cells of the bone-marrow, the red corpuscles are increased in number concomitantly with the volume of adrenoxidase in the blood.*

The physiological action of iron is at present unknown. The increase of general oxygenation has been noted by various observers, and by some after the first dose. Wood[390] says: "The studies of Pokrowsky[391] have shown that, in cases of anæmia, after the exhibition of iron the temperature does rise, even when in the beginning it was not below normal, and that simultaneously there is an increase in the daily elimination of urea"—experiments confirmed by Botkin in healthy men. "The increased oxidation cannot be due simply to an increase in the number of corpuscles," continues Prof. Wood, "for while the latter accrue slowly, Pokrowsky found that the temperature sometimes rose within five hours after the exhibition of the first dose." Von Noorden[392] also states that "the salts circulating in the blood (medicinal iron) exert a powerful stimulus upon the hæmatopoietic cells of the bone-marrow, and the result of this stimulation is an improvement of the blood."

A second important effect of iron is to increase the proportion of hæmoglobin. This metal is the main component of hæmatin, the coloring constituent of hæmoglobin that remains in the red corpuscles; it serves to hold the albuminous portion of the hæmoglobin, *i.e.*, the adrenoxidase, within these cells, pending its distribution.* While the adrenal center and the bone-marrow are being stimulated, therefore, as stated above, the iron itself is absorbed by the red corpuscles to form hæmatin, and this pigment, owing to its affinity for adrenoxidase, forms hæmoglobin—or, rather, oxyhæmoglobin.*

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* *Author's conclusion.*

[390] Wood: *Loc. cit.*, thirteenth edition, p. 446, 1906.

[391] Pokrowsky: Virchow's Archiv, Bd. xxii, S. 476, 1861.

[392] von Noorden: "Nothnagel's Encyclo.," vol. on the Blood, p. 487, 1905.

The remarkable way in which iron increases the formation of hæmoglobin, in chlorosis for instance, is as well known as is the fact that it is the most important constituent of hæmatin. As to its functional connection with adrenoxidase, the reader is referred to the thirteenth chapter. We have seen that iron is taken up mainly from the duodenum by leucocytes; additional evidence to this effect was recently contributed by Matzner.[303] It is then, as shown by many investigators, including Wöltering[304] and Macallum,[305] deposited in the liver, where, according to Wöltering, Kunkel[306] and others, it undergoes changes that fit it for the formation of hæmoglobin. The researches of Quincke,[307] W. S. Hall,[308] Schmey[309] and others have shown that besides the portion converted into hæmoglobin, any excess of iron was stored in the liver itself, the spleen and the muscles, particularly the myocardium. I have submitted in the first volume evidence suggesting that part of the iron in the liver was carried by eosinophile leucocytes to the capillaries of the alveoli, where it was absorbed by red corpuscles along with the albuminous portion of hæmoglobin, the adrenoxidase.

The presence of iron in chromatin, the living substance of cells, and in the nucleo-proteid out of which it is built, points to a third important action when this metal is administered to subjects in which it is actually deficient:* being endowed with marked catalytic properties, iron probably serves as a catalytic. The red corpuscle being a living cell, its hæmatin, owing to its rich iron content, is its nucleus. The normal elaboration of hæmoglobin is carried on through the iron-laden chromatin of nuclei derived from meats, fruit, vegetables, etc., which thus becomes the mother-substance or "hæmatogen" of hæmoglobin. But once in the corpuscle, the life or working efficiency of its hæmatin (which remains in the cell) must be maintained. Its iron fulfills the identical rôle that the adrenal principle does in the tissue-cell, viz., the albuminous portion of the hæmoglobin (the adrenoxidase), to which it is linked, serving as source of oxygen, the catalytic process continues uninterruptedly until the corpuscle itself is worn out and destroyed.*

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* *Author's conclusion.*

[303] Matzner: Die Heilkunde, 1903.

[304] Wöltering: Zeit. f. phys. Chemie, Bd. xxi, S. 186, 1896.

[305] Macallum: Jour. of Physiol., vol. xvi, p. 268, 1894.

[306] Kunkel: Archiv f. d. ges. Physiol., Bd. lxi, S. 595, 1895.

[307] Quincke: Sajous's "Annual of the Univ. Med. Sci.," vol. v, a-95, 1896.

[308] Hall: Archiv f. Anat. u. Physiol., Physiol. Abth., S. 49, 1896.

[309] Schmey: Hoppe-Seyler's Zeit. f. physiol. Chemie, Bd. xxxix, S. 215, 1903.

Hammarsten refers to the now familiar fact that "the nucleo-proteids contain iron," and that the ash of muscle (meat) contains from 0.04 to 0.1 per 1000 parts.[310] Iron was found in chromatin by Macallum,[311] in the chromatin granules, fibrils and nodal points of the chromatin network in the nuclei of animal and vegetable cells examined, and sometimes in the cytoplasm. Molisch[312] found that in the absence of iron, plants fail to form chlorophyll. The presence of assimilated iron was discerned by Macallum even in the lowest forms of life, the protozoa. Bunge had been led to conclude that the chromatin of plants was the mother-substance of hæmoglobin; Macallum reached the same conclusion as regards both animal and vegetable chromatin.

The catalytic property of iron is now generally recognized. A. Robin and Bardet[313] conclude in this connection that "all the researches of recent years tend to demonstrate that soluble oxides and the metals themselves, when in the colloidal state, can fulfill the part of ferment." As the albuminate formed in the stomach is a colloid and the adrenoxidase converts the organic iron ingested into an oxidase, we have the conditions required for this purpose.* Referring to the function of this ferment, Robin and Bardet remark: "One should say, in truth, that they are catalytic ferments," which "borrow from the left to deal out to the right."

Poisoning.—Poisoning by iron ingested by the mouth is rendered practically impossible by the fact that it is absorbed very slowly, the rest passing out by the intestinal canal. Attempts have been made to ascertain its toxic effects by injecting iron salts, such as the tartrate of iron and sodium, into animals. But introduced in this artificial manner, iron fails to undergo the preliminary gastro-intestinal treatment which prepares it for physiological assimilation.* The results, therefore, are apt to be misleading and are, at best, purely of academic interest.

Therapeutics.—Iron is chiefly used in *anæmia*, and particularly in *chlorosis*. As will be shown in the article on Anæmia, however, it is indicated in a limited number of cases, depression of the functional efficiency of the vasomotor and adrenal centers accounting for the majority of instances in which pallor, muscular weakness, etc., are witnessed.* In the cases of true anæmia, those due to food containing an insufficient quantity of iron, its effects are, of course, striking, as they are in chlorosis. This is readily accounted for in view of the cardinal functions this metal fulfils in the economy.

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* *Author's conclusion.*

[310] Hammarsten: *Loc. cit.*, p. 402, 1904.

[311] Macallum: *Loc. cit.*, and Rep. of Brit. Assoc. Adv. of Sci., vol. 1896.

[312] Molisch: Sitz. Wien. Akad., Bd. ciii, Abt. i, S. 554, 1894.

[313] Robin and Bardet: Bull. gén. de thérap., Feb. 25, 1905.

PHOSPHORUS.

Physiological Action.—The rôle of phosphorus in the *organism is of cardinal importance in view mainly of its identity as a component: (1) of the nuclein of all cells, including the* leucocytes;* (2) of the nucleo-proteid *granulations which these cells secrete into the tissue cells to take part in their vital interchanges, and into the blood, to sustain (with adrenoxidase) its normal temperature;* (3) of the thyro-parathyroid ferment, thyroidase;* (4) of the myelin of nerves, which, with the adrenoxidase circulating in the axis-cylinders* and their networks in the myelin, generates the nerve-impulse;* (5) of the cell-bodies of all neurons and their dendrites as chromatin, sustaining therein (with their oxychromatin, adrenoxidase) their vitality and functional activity, as it does in all other cells;* (6) of bones, chiefly in the form of calcium phosphate.

The human organism acquires its phosphorus in organic combination from animal and vegetable foods, and it is in such a combination that phosphorus is absorbed. When, therefore, it is administered in an assimilable form in disorders due entirely or partly to deficiency of this element in either or all of the organic bodies enumerated above, it can, in suitable cases, restore function.

The important functions I ascribe to phosphorus were reviewed in the fifteenth chapter, to which the reader is referred. The far-reaching rôle of this element in the organism which the foregoing statements indicate, is well shown by experiments of Forster[224] in dogs, which led this author to conclude that deprivation of phosphorus proved fatal more rapidly than actual starvation. The animals were fed on meat from which all the phosphorus in organic combination was as much as possible removed artificially. The animals soon reached a condition of extreme exhaustion. Conversely, Pouchet and Chevalier,[225] referring to the effects of organic compounds of phosphorus, state that "they increase nutrition, as shown by increase of weight; ameliorate nervous activity and muscular tonus; increase the percentage of hæmoglobin—all phenomena which indicate marked synthetic assimilation under the influence of these compounds."

The therapeutic effects of phosphorus are best obtained by administering this element in organic combination, the glycerophosphates for instance. When phosphorus or any of its oxidizable preparations is used, it becomes oxidized in the stomach by the adrenoxidase of the gastric juice, or in the intestine by that of the intestinal juice.* It is then absorbed as hypophorous or phosphoric acid, an inert substance which the organism eliminates as a useless waste along with the phosphoric acid derived from tissue metabolism. Hence the frequency with which phosphorus proves of no therapeutic value.

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* *Author's conclusion.*

[224] Forster: Zeit. f. Biol., Bd. ix, S. 297, 1873.

[225] Pouchet and Chevalier: Bull. gén. de thérap., Dec. 30, 1905.

Cushny[326] states that "the fate of phosphorus in the body is still obscure," but that "it is possible that some of it is oxidized to phosphoric acid." Ranvier[327] found that when phosphorus was introduced under the skin, the only result was arrest of local nutrition. Being endowed with intense affinity for oxygen, it obviously depletes the neighboring tissues of theirs and becomes itself oxidized. Cau[328] also found that phosphorus was oxidized by the tissues. The presence of adrenoxidase in the tissue fluids fully accounts for this, since it forms part, as we have seen, of the gastric secretions. The oxidized portion of what phosphorus is ingested loses its toxicity, for, as stated by Cushny, "as soon as it is oxidized, phosphorus loses its specific action, all the acids being comparatively harmless." This has been emphasized by the researches of Bókay,[329] Stassano and Billon,[330] Frenkel[331] and others. The last-named author found that, "contrary to the affirmations of the partisans of phosphoric acid, the latter is incapable of assimilation by the economy, and is excreted in its totality."

Untoward Effects and Acute Poisoning.—The presence of adrenoxidase in the blood* explains many facts which so far have remained obscure.*

If the dose of phosphorus is sufficiently small, it may all be oxidized and prove harmless. When, however, the dose is large, the secretions are not alone deprived of their oxygen,* but the cellular elements of the gastric mucous membrane likewise. Severe gastric pain, eructations of gas emitting a strong odor of garlic occur, and the patient experiences a sensation of heat along the œsophagus, with great thirst, headache, nausea, vomiting, the vomitus being often luminous in the dark —all due to a severe gastro-adenitis thus excited. Erosions may involve the local vascular supply and entail the presence of blood in the vomited material. What portion of the phosphorus remains unoxidized on passing down to the intestine excites therein corresponding lesions, even the colon being involved in the morbid process. The violent burning pain in the epigastrium gradually extends throughout the entire abdomen; diarrhœa develops rapidly into violent purging, the dejecta likewise being phosphorescent in the dark, and sometimes bloody. At times the local inflammatory process is so severe that reflex excitation of the intestinal glandular elements and muscles can no longer occur and constipation results.

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* *Author's conclusion.*

[326] Cushny: *Loc. cit.*, fourth edition, p. 601, 1906.

[327] Ranvier: Cited by Manquat: *Loc. cit.*, vol. i, p. 969.

[328] Cau: Thèse de Paris, 1901.

[329] Bókay: Zeit. f. physiol. Chem., Bd. i, S. 157, 1877-78.

[330] Stassano and Billon: C. r. de la Soc. de biol., T. lv., p. 482, 1903.

[331] Frenkel: Le progrès méd., Mar. 3, 1906.

The well-known gastric lesions are duplicated in the intestinal canal. Plavec[222] found experimentally in dogs that phosphorus caused hæmorrhagic injection of the duodenal mucous membrane, and in some instances ulceration. In an acute case reported by Newey,[223] the stomach, which contained eight ounces (250 gms.) of blood, showed areas of softening and ulceration. The entire intestine presented corresponding signs, the transverse colon being intensely inflamed. The vascular engorgement observed even in acute cases is not due to the local action of the poison alone, however, as is shown below.

Death may occur suddenly during this, the acute stage, but it is due to a cause differing entirely from that which entails a fatal issue when the case is prolonged, namely, reflex inhibition of the heart,* by excessive (sympathetic) constriction of its arterioles.* This organ becomes suddenly very weak, the pulse likewise; the pupils are widely dilated, and coma and death soon follow.

Wood[224] states that "in the very acute cases of phosphorus-poisoning a primary condition of pronounced cardiac weakness, passing into paralysis, may be present." Witherstine[225] refers to a case in which death occurred in half an hour. Chtchebrak[226] found that the first action of the drug was to increase the rapidity of the circulation and to raise the blood-pressure, this being immediately succeeded by a decline of vascular tension. As inhibition of the heart is due to excessive vasoconstriction of its arterioles,* the preliminary rise of blood-pressure indicates how phosphorus can provoke cardiac paralysis.

In the majority of cases, the symptoms, after a period of acute suffering, lasting from a few hours to two days, abate, and recovery apparently occurs. After one or more days of relative comfort, however, the acute symptoms reappear. But now the pain extends to the liver, which organ may be found to be enlarged, and the vomiting often contains "coffee-ground" material, *i.e.*, altered blood. The stools, if diarrhœa prevails, are occasionally bloody and are apt to be clay-colored, the latter fact indicating the absence of bile. Neither the vomited material nor the stools are phosphorescent at this stage—evidence to the effect that the greater part, at least, of the phosphorus (the unoxidized remnants) has been gradually absorbed into the circulation, and that the dejecta now contain only phosphorus oxides.

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* *Author's conclusion.*

[222] Plavec: Arch. f. exp. Path. u. Pharm., Bd. xlviii, S. 150, 1902.

[223] Newey: Lancet, Sept. 22, 1900.

[224] Wood: *Loc. cit.*, thirteenth edition, p. 461, 1906.

[225] Witherstine: Sajous's "Annual and Analyt. Cyclo.," vol. v, p. 471, 1900.

[226] Chtchebrak: "Les Bactéries," Paris, 1891.

As previously stated, a portion of the phosphorus is oxidized in the alimentary canal by the oxidizing substance of its secretions. "It has of late years been demonstrated," says Wood,[227] "that phosphorus passes into the blood as *phosphorus*, and not in the form of phosphoric acid or other compound." Wegner,[228] Husemann and Marmer, Dybkowsky[229] and others have found phosphorus not only in the blood and liver, but also in practically all tissues. On the other hand, Poulet[230] has ascertained that it was eliminated as hypophosphoric acid, while Santesson and Malmgren[231] observed after administering large doses of phosphorus sesqui-sulphide to rabbits, a remarkable excess in the output not only of nitrogen, sulphates and ammonia, but also of phosphoric acid.

The recurrence of acute symptoms marks the beginning of the so-called "subacute" stage, a time when the blood's functional activity has become impaired mainly by active hæmolysis.* This is due to the fact that the phosphorus-laden nucleo-proteid of the plasma is supplemented by the phosphorus absorbed from the alimentary canal.* The simultaneous presence of an excessive proportion of phosphorus and adrenoxidase in the blood-plasma, by liberating heat-energy to an unusual degree, correspondingly enhances the proteolytic activity of the blood's trypsin, and hæmolysis, *i.e.*, destruction of the red corpuscles, occurs.* As an inordinate proportion of adrenoxidase is utilized in the process and the coagulating properties of the blood are due to this substance (which is, we have seen, the "fibrin ferment"), the blood itself loses its coagulating properties.* It becomes unduly fluid, and, passing readily through the capillary walls, ecchymoses occur in various parts of the body, besides, in many instance, hæmorrhages from the nose, uterus, in the retina, and occasionally gangrene. The normal result of such a condition of the blood soon shows itself, *i.e.*, great weakness, collapse, and death by cardiac failure—often preceded by convulsions caused by the accumulation of

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* *Author's conclusion.*

[227] Wood: *Loc. cit.*, eleventh edition, p. 438, 1900.

[228] Wegner: Virchow's Archiv, Bd. lv, S. 11, 1872.

[229] Dybkowsky: Hoppe-Seyler's Med.-Chem. Untersuchungen, H. i, S. 54, 1866.

[230] Poulet: Gaz. méd. de Paris, Aug. 17, 1872.

[231] Santesson and Malmgren: Skand. Arch. f. physiol., Bd. xv, S. 259, 1904.

toxic wastes which the deficiency of adrenoxidase in the blood entails.*

Corin and Ansiaux[232] ascertained that "fluidity of the blood is found only in cases of phosphorus-poisoning which have followed a *subacute course.*" When *introduced into the blood-stream, phosphorus is* independent therein of the synthesis of nucleins, *for Röhmann*[233] *found* that inorganic phosphorus compounds were hardly used at all. *It is, therefore, as surplus to the* nucleo-proteid's phosphorus that it occurs in *the blood—the* aggregate thus becoming pathogenic by increasing, with the adrenoxidase, general metabolism. That this actually occurs is shown by the *fact* that there is, as stated by Cushny,[234] "a very considerable increase in the nitrogen" during this stage, "even although the patient continues *to fast.*" That red corpuscles are destroyed during this process has been emphasized by the investigations of Vogel[235] in birds; the hæmolysis began the second day, and by the sixth the comparative blood-count showed that one-half of the red corpuscles had been destroyed. Similar experiments in mammals (dogs) by d'Amore and Falcone[236] gave similar results. Wood[237] refers to Concato as having shown that the red corpuscles were "diminished in size and altered in form"—proof that they were undergoing destructive metamorphosis.

The fluidity of the blood is evidently a feature of the subacute stage. Cevidalli[238] found that in order to render the blood uncoagulable in dogs, phosphorus had to be injected from five to ten days. Again, it is undoubtedly to the destruction of adrenoxidase (the fibrin ferment) that the fluidity of the blood is due. Cevidalli also observed a "gradual diminution and disappearance of the coagulating ferment." The lethal phenomena are obviously, under these conditions, due to the same cause: Cushny,[239] referring to Araki,[240] remarks: "In the statement that lack of oxygen plays a part in phosphorus-poisoning, he only confirms the impression of many earlier writers."

A striking symptom of the subacute stage is jaundice, first of the conjunctivæ, then of the whole body, which may appear from thirty-six hours to several days after ingestion of the poison. This is the result of several factors. The phosphorus from the alimentary canal having first to pass through the liver, it provokes therein a process identical to that in the blood; here, however, the red corpuscles are not alone attacked, but the hepatic structures *per se* likewise, and necrotic foci are formed in various parts of the organ.* Hence the fact that it becomes enlarged and painful. At first the activity of the liver-cells is greatly enhanced, as shown by a marked increase in the pigment excreted—"pigment," meaning here bilirubin and hæmatoidin, both of which, we have seen, are reduced adrenoxidase.* Finally, the bile thickens, owing to the presence therein of its usual constituents, and also of cellular detritus, broken-down corpuscles, etc.—all of which contribute to block the biliary passages. Jaundice appears at this time.

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* *Author's conclusion.*

[232] Corin and Ansiaux: Vierteljahresschrift f. gerichtliche Med. u. Sanitäts., S. 80, 212, 1894.

[233] Röhmann: Berl. klin. Woch., Bd. xxxv, S. 789, 1898.

[234] Cushny: *Loc. cit.*, fourth edition, p. 590, 1906.

[235] Vogel: Arch. intern. de pharm. et de thérap., T. x, fasc. iii et iv, 1902.

[236] d'Amore and Falcone: Arch. de pharmacod. de Gand, vol. i, p. 247, 1894.

[237] Wood: *Loc. cit.*, thirteenth edition, p. 436, 1906.

[238] Cevidalli: Riforma Med.; Phila. Med. Jour., Feb. 7, 1904.

[239] Cushny: *Loc. cit.*, third edition, p. 602, 1899.

[240] Araki: Zeit. f. physiol. Chem., Bd. xvii, S. 311, 1892-93; Bd. xix, S. 422, 1894.

By "jaundice" here is meant a condition due to the resorption into the general circulation of reduced adrenoxidase that should have passed out with the bile.* On reaching the skin, this substance, by a process similar to that which prevails in the pathogenesis of bronzing, gives it its yellow hue—an early stage of melanosis.* The reduced adrenoxidase is at the time, and even before, found in the urine as "bilirubin" or "hæmatoidin."

That destruction of the hepatic tissues is due to the action of some autolytic ferment has been suggested by Jacoby.[241] He also noted the disappearance of fibrinogen from the hepatic blood; this substance, we have seen, is composed of nucleo-proteid fibrinogen proper and adrenoxidase (fibrin ferment). The destructive process in the liver is a familiar pathological fact. Podwyssotsky[242] found necrotic foci in this organ. West[243] found the hepatic cellular elements converted into a fine granular detritus amidst which the nuclei could hardly be detected. Cushny[244] states that "the jaundice may also be accounted for in part by the destruction of the red cells of the blood and consequent increase of pigment formation in the liver." The intra-corpuscular constituent of hæmoglobin (which only leaves them under abnormal conditions, one of which is when the corpuscles are broken up) is, we have seen, hæmatin. Wood[245] states that "hæmatin crystals are occasionally found in the viscera." Demarbaix and Wilmart,[246] moreover, found hæmatoidin (adrenoxidase) in the urine. The sequence of events given above was traced in dogs with great assiduity by Stadelmann.[247]

The engorgement of the biliary passages, besides deflecting into the hepatic veins what reduced adrenoxidase should have passed out with the bile, thus causing its return to the blood-stream,* simultaneously provokes engorgement of the entire vascular system. The vessels, whose walls tend already to dilate owing to the lowered metabolism in their muscular walls incident upon the hæmolysis and deficiency of adrenoxidase in the blood *per se*, are thus submitted to centrifugal pressure and still further dilated.* The cerebral vascular system, including its cellular elements, becoming hyperæmic,* headache, restless and dreamy sleep or wakefulness are complained of. If the cerebral congestion becomes very great,* wild delirium may occur. A similar condition of the spinal system* may evoke disorders of sensation, particularly of the temperature sense, hyperalgesia, pains suggesting neuritis, muscular twitchings, localized spasms or even general convulsions, the latter being often the precursors of death.

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* *Author's conclusion.*

[241] Jacoby: Zeit. f. physiol. Chem., Bd. xxx, S. 174, 1900.

[242] Podwyssotsky: St. Petersburg med. Woch., Bd. xiii, S. 211, 1888.

[243] West: Lancet, Feb. 4, 1893.

[244] Cushny: *Loc. cit.*, fourth edition, p. 598, 1906.

[245] Wood: *Loc. cit.*, thirteenth edition, p. 464, 1906.

[246] Demarbaix and Wilmart: Presse méd., vol. xxi, p. 25, 1899.

[247] Stadelmann: Archiv f. exp. Path. u. Pharm., Bd. xxiv, S. 270, 1888.

In cases that recover, the phosphorus available in the intestine has finally been either oxidized, eliminated or absorbed; the destruction of red corpuscles and hepatic cellular elements then ceases. The bile gradually losing its viscidity, the accumulated detritus is voided into the intestine and eliminated; and the skin "pigment" being absorbed, relatively normal conditions are restored, though the patches of destroyed tissue in the stomach and liver may become the seat of interstitial connective-tissue proliferation. In the liver, this may assume the type of a true cirrhosis with atrophy of the organ. Digestive and nervous disorders often persist some time after recovery.

A striking feature of the morbid process is the presence of fatty degeneration in all organs, including the smallest arterioles of the spinal cord. The so-called "fat" here is a mixture of blood-constituents, fibrin, nucleo-proteid, etc., formed when the supply of adrenoxidase is inadequate to maintain the temperature and fluidity of the blood.* It is a post-mortem phenomenon corresponding in a measure with that of myosin formation.*

That the blood-pressure is lowered has been observed by a number of investigators. Schiff[348] years ago noted that the arteries were so widely dilated after death from phosphorus-poisoning, that the veins were comparatively empty. Pal[349] ascribed this vasodilation, not to the weakened cardiac power, but to dilation of the vessels themselves. Cornil and Brault[350] ascribe the lesions found in the interstitial process in the vascular walls and the organs in general to a *sui generis* fatty process, *i.e.*, one preceded by no inflammation, and beginning six or seven hours after the ingestion of the poison and terminating four to seven days thereafter. Vollbracht,[351] in accord with these observations, found the vascular walls degenerated and associated with gangrene of both extremities.

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* *Author's conclusion.*

[348] Schiff: *Ibid.*, Bd. ii, S. 345, 1874.

[349] Pal: Wien. klin. Woch., Bd. ix, S. 909, 1896.

[350] Cornil and Brault: Manquat: *Loc. cit.*, vol. i, p. 972, 1903.

[351] Vollbracht: Wien. klin. Woch., Bd. xiv, S. 1238, 1901.

The "fatty degeneration" of phosphorus-poisoning is due, as elsewhere, to a deficiency of adrenoxidase.* After referring to the older view, that lessened oxidation of proteid fats explained fatty degeneration, as inconsistent with known facts, Cushny[illegible] remarks: "Lessened oxidation and fatty degeneration occur together under so many conditions, however, that there must almost certainly be a causal relation between them, though it is impossible to state at present its exact nature."

Chronic Phosphorus Poisoning.—This form of poisoning, observed usually among persons employed in the manufacture of white sulphur matches, differs from the acute form in that the quantity inhaled at a given time is inadequate to provoke acute phenomena. The continued absorption from the respiratory surfaces, however, finally gives rise to practically all the symptoms already enumerated, the most common of which are weakness, abdominal pains, anorexia, a garlicky breath, gastric disorders, diarrhœa or obstinate congestion, a subicteric color of the skin, wasting, etc. These cases differ from those of the acute type, in that they suffer from necrosis of the lower jaw. This condition has been found to be the result of penetration of phosphorus-fumes to this bone through the intermediary of carious teeth. This process is readily explained when the fact that bony tissues are dependent, like all others, upon adrenoxidase for their oxygen, is taken into account: the nutrient plasma of the bone being deprived of its oxygen by the phosphorus, which has a greater affinity for it than the bone itself, the latter, no longer nourished, dies.*

Wegner[illegible] found that rabbits kept in phosphorus-fumes suffered in no way from necrosis if their teeth were sound, but that injuries in which the jaw-bone could be reached by the fumes were followed by periostitis and necrosis. Magitot[illegible] observed that phosphorus-workers supplied with perfect teeth were free from necrosis even after years' employment at this occupation, while all those who had bad teeth suffered from necrosis.

The *treatment of phosphorus poisoning* is described in a special section at the end of this volume.

Therapeutics.—The physiological function I have ascribed to phosphorus in the tissue-cells (including nerve-cells) and blood, viz., to liberate heat-energy by combining with oxygen of the adrenoxidase,* places this element among our chief resources as a therapeutic agent, since it constitutes one of the pillars of the vital process itself.* By the use of strychnine, digitalis, coca, etc., we greatly stimulate functional activity, but the judicious adjunction to them of substances which actually take part in function, such as phosphorus, iron, appropriate foods, etc., we supply besides, the building material.* It is as such that phosphorus is especially beneficial in *neurasthenia* due to overwork, anxiety, mental strain and sexual excesses. Here, it actually replaces missing materials.* In *anæmia*, the addition of phosphorus to iron will render the latter effective where before it was useless, because the improvement of the oxygenizing power of the blood requires a corresponding increase of available nuclein.* In *impaired nutrition* following exhausting diseases, such as influenza, typhoid, typhus, intermittent fevers, etc., the same indication prevails. This applies likewise to debility following *prolonged lactation, overwork, shock, sorrow,* etc. In the disorders which are thought to be normal results of old age, such as *loss of memory, mental torpor, insomnia,* etc., an inadequate supply of phosphorus, iron and iodine, is the pathogenic factor, and these agents will often serve to prolong a useful life. In the depraved condition to which *morphinomania* and *chronic alcoholism* finally drive the patient, the judicious use of phosphorus after cessation of the habit is conquered, not only hastens recovery, but tends to prevent its recurrence by enhancing the nutrition and conductivity of all nerves.* Finally, the value of phosphorus in *rickets* and *osteomalacia* is generally recognized.

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* *Author's conclusion.*

[illegible] Cushny: *Loc. cit.*, third edition, p. 606, 1899.

[illegible] Wegner: Virchow's Archiv, Bd. lv, S. 11, 1872.

[illegible] Magitot: C. r. de l'Acad. de méd., Mar. 12, 1886.

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* *Author's conclusion.*

CHAPTER XX.

THE INTERNAL SECRETIONS IN THEIR RELATION TO PHARMACODYNAMICS (*Continued*).

THE SYMPATHETIC CENTER AS THE SLEEP CENTER.

Bradbury, in his Croonian Lecture,[1] stated eight years ago, that "notwithstanding the brilliant and laborious researches of physiologists and neurologists during recent years, the phenomenon of sleep is still enveloped in mystery"—a conclusion which is still applicable. The reason for this is plain in view of the fact pointed out by myself in the first volume, that this function is intimately connected with the circulation of oxidizing substance (adrenoxidase) *in* the neurons and their dendrites, that sleep is due to a diminution of this substance in these elements, and that the adrenal system is intimately connected with this process. To overlook this intrinsic nervous circulation and the ductless glands in this connection is to perpetuate the "mystery" to which Bradbury refers. And this applies not only to the mechanism of sleep, but also to a widespread source of suffering, insomnia, and, moreover, to the action of hypnotics and anæsthetics.

A diminution of adrenoxidase in the nervous elements referred to entails a corresponding reduction of metabolic activity and other phenomena connected therewith. Howell[2] wrote recently: "The central and most important fact of sleep is the partial or complete loss of consciousness, and this phenomenon may be referred directly to a lessened metabolic activity in the brain tissue, presumably in the cortex cerebri." Again, "the physiological oxidations are also decreased, as shown by the diminished output of carbon dioxide." A fall of blood-pressure is also present, as shown by Tarchanoff[3] in dogs and by Brush and Fayerweather[4] in man.

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[1] Bradbury: Lancet, June 24, 1899.
[2] Howell: "T. B. of Physiol.," p. 228, 1905.
[3] Tarchanoff: Arch. ital. de biol., vol. xxi, p. 318, 1894.
[4] Brush and Fayerweather: Amer. Jour. of Physiol., vol. v, p. 199, 1901.

The manner in which hypometabolism produces sleep and the process through which lowered oxygenation of the cortex is produced are left unexplained by the prevailing interpretations. In the first volume, I filled both these gaps. In the first place, I showed that the adrenoxidase-laden plasma which circulates in all parts of the neuron sustained the vital process in this organ as it does in all cells.[5] and submitted the conclusion[6] that the thornlike processes which project from the dendrites[7] and other parts of a neuron, *i.e.*, the gemmules, were "peripheral extensions of the dendritic walls having for their purpose to increase, when *erect*, the area of myelin exposed to the action of the oxidizing substance [adrenoxidase] of the plasma, and thus to render the dendrite functionally active, *i.e.*, able to transmit or receive nervous impulses;" and also that when the gemmules are retracted or collapsed, "functional activity is in abeyance, as during *sleep*, anæsthesia, etc." Additional evidence has been submitted in the present volume as to the rôle of adrenoxidase and myelin in all nerve-cells, and to the effect that they jointly liberated nerve-energy, *i.e.*, the impulse. The manner in which sleep follows thus becomes plain: the *intrinsic* metabolism of all nervous elements, including those of the cortex, is itself reduced.

The introduction of adrenoxidase and myelin as the joint source of functional activity harmonizes with a theory to which Bradbury refers as follows: "The most fascinating of them all is what Duval has termed the histological theory of sleep: This seems to have been propounded in its most rudimentary state by Rabl-Rückhard, who suggested that an assumed amœboid motion of the neurons, and especially the dendritic processes, would account for various psychological phenomena. Thus sleep might be explained by a *retraction of these processes* and consequent *inability of nervous impulses to pass from one neuron to another*. The same theory was elaborated independently by Lépine and Duval. Lépine thinks this isolation of the individual neurons may be due to some chemical modification of the cellular protoplasm, and he also states that the theory explains the extraordinary suddenness with which a state of wakefulness passes into one of sleep. Duval goes so far as to explain the action of medicaments on this theory, and he draws comparisons between the action of drugs on the terminal dendritic processes and the effect of curare on motor nerve-endings. This is surely hypothetical" . . . . quite as much so, I would add, as the assumed action of curare (administered internally) on nerve-endings, as emphasized in the preceding chapter.

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[5] *Cf.* vol. I, pp. 518 to 590 incl.
[6] *Cf.* vol. I, p. 577.
[7] *Cf.* vol. I, plate opposite p. 550.

The manner in which adrenoxidase and myelin take part in the transmission of impulses from neuron to neuron, suggests itself when the effect of intrinsic metabolic activity on its gemmules is taken into account. Ramon y Cajal,[8] who states that the dendrites are covered with a "protective sheath of great tenuity" (which I assimilate to the myelin sheath of nerves, and a factor in the elaboration of nervous energy as stated above), advanced the view that impulses were transmitted by the gemmules which project through this sheath. As previously stated, however, and for reasons submitted in the first volume, I ascribe a different function to these thorn-like projections, viz., to extend the area of myelin exposed to the action of adrenoxidase and local metabolic activity. The structures which I regard as intermediaries for the transmission of impulses, afferent or efferent, are the tips of the dendrites and the branches (and collaterals) given off by the axons or axis-cylinders of neurons, to which Berkley[9] refers as a "bulbous ending situated upon the extremity of the finest branches of the nerve-fibers." Since he says of the latter: "The researches of Flechsig, as well as my own, have shown that these fine branches are furnished with a thin layer of myelin nearly to their termination." and as they likewise take methylene blue and other stains showing the presence of adrenoxidase, the bulbous tips referred to are, as well as those of the dendrites and their thorns or gemmules, subject to erection during activity as distinguished from rest, *i.e.*, sleep.

Now, whether with Cajal we regard the gemmules as the structures which receive impulses from these bulblike axon terminals, or with Berkley, that the latter transfer them to the dendrites between the gemmules, or with me, that the bulbous tips of the dendrites (as in nerve-terminals in the Pacinian corpuscles, in the end-bulb of Krause, etc.) receive the impulses from the knobbed axon-terminals or offshoots from dendrites, the mechanism of transmission is the same, provided another conclusion embodied in the first volume (in accord with Berkley's previous observation) be accepted, namely: that these end-organs do not actually touch each other, as believed by some, but that they are separated by[10] an infinitesimal distance. Now, as I interpret the process, during active metabolism, *i.e.*, during waking hours, this infinitesimal distance is preserved, because *both dendritic and axonal terminals are erect.* The functions of the brain are active, owing to the ability of these terminals to *touch and separate with great rapidity,* i.e., *to vibrate rhythmically* according to the nature of the stimulus transmitted, whether it be connected with motility, sensibility or thought. Conversely, during lowered metabolism the bulbous terminals recede and are then separated sufficiently to prevent vibratory contact and inhibit function. Motility, sensibility and thought are then in abeyance, *i.e.*, in the state of rest or sleep.

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[8] Ramon y Cajal: Cited by Bradbury: *Loc. cit.*
[9] Berkley: Johns Hopkins Hosp. Reports, vol. vi, p. 89, 1897.

Thus it is that lowered metabolism can, in the light of my views, produce sleep.

Another factor is required in this connection, however, to account for the mechanical erection of the gemmules and the bulbous tips, namely, an increase of blood-pressure. The anæmia of the cerebral structures observed in exposed areas and other facts have caused Howell[11] to suggest a theory which has deservedly received considerable attention, the "vasomotor" theory. The reduction of blood affords the necessary factor for the recession of the bulbous tips during sleep, and their erection during wakefulness. While he explains this phenomenon by variations in the cutaneous circulation, Leonard Hill[12] accounts for it by dilation of the vessels of the splanchnic area, a condition which, we have now seen repeatedly, causes recession of blood from the periphery—and from the brain, according to Hill. The *manner* in which this vasodilation is brought about, however, is left obscure by these investigators. And yet, a fully established factor of the problem clearly accounts for it, viz., lessened metabolic activity, which, as previously stated, affects the cardiac muscle and the vascular muscle fibers, two conditions which entail vascular relaxation.

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[10] *Cf.* vol. i, p. 579.

[11] Howell: Jour. of Exper. Med., vol. ii, No. 3, 1897.

[12] Leonard Hill: "The Physiol. and Pathol. of the Cerebral Circulation, London, 1896.

That this brings the original cause of sleep down to the organs which regulate metabolism is self-evident. In the first volume, I ascribed[13] retraction of the gemmules to "suprarenal insufficiency." By stating[14] therein that "when the gemmules are retracted or collapsed, functional activity is in abeyance as during sleep . . . . ," I indicated that sleep was to be ascribed primarily to a deficiency of adrenal secretion, *i.e.*, of adrenoxidase. This relegates us to the adrenal center in the pituitary body.

Salmon has recently[15] suggested that the internal secretion of the pituitary body produces sleep. All the evidence extant indicates, however, that this organ enhances oxidation; it fails, therefore, to support such a theory. Again, I have called attention to the fact that in the higher vertebrates the pituitary body was not a secretory organ, its secretory functions having been taken up by its offshoots, the adrenals.

Quite in keeping with the prevailing knowledge concerning the rôle of hypometabolism in sleep, and my own view that *depression* (and not overactivity, as Salmon believes) of the functions of the adrenal center, is the important fact pointed out by Lorand,[16] that degeneration of the thyroid gland causes a tendency to sleep. He observed that dogs deprived of their thyroid slept almost all the time, that the loudest noises failed to awake them, and adduces other facts in support of his opinion. Recalling the researches of Magnus Levy, Thiele, Nehring and others to the effect that the thyroid gland regulates metabolism, Lorand ascribes the influence of degeneration of this organ on sleep to a corresponding depression of general metabolism. The manner in which this process is carried out is fully explained by the functions I had attributed to the thyroid secretion in the first volume, viz., to stimulate the adrenal center of the pituitary body, and through it the adrenals, whose secretion becomes converted into adrenoxidase in the lungs. It is plain that under these conditions and as Lorand has shown, any degenerative disorder of the thyroid should depress the adrenal center, inhibit the formation of adrenoxidase and metabolism, and provoke sleep.

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[13] *Cf.* vol. i, p. 530.

[14] *Cf.* vol. i, p. 578.

[15] Salmon: Trans. 15th Congress of Intern. Med., Genoa, Oct., 1905.

[16] Lorand: Verhandl. d. Congr. Innere Med., Bd. xxii, S. 306, 1905.

Interpreted from my standpoint, however, this does not represent the process which prevails in normal or *physiological* sleep. It is sleep due to a pathological condition. The thyroid, as a gland, can not be a governing organ: as is the case with the adrenals and all other glands, its secretory activity is regulated by a nerve-center.

In a preceding chapter[17] I pointed out that it was by inhibiting the functions of the pituitary body and of the thyroid gland that Cyon's depressor nerve produced general vasodilation, at first of the vessels of the splanchnic area and then the vessels of the peripheral structures. The main conditions of Howell's vasomotor theory and Hill's observations are thus met. The manner in which metabolism is depressed during sleep is now self-evident: the proportions of thyroidase, which sensitizes all cells, and of adrenoxidase, which incites and sustains metabolism, being reduced, the blood's energizing properties are brought down to the physiological limit which normal sleep requires. This entails just sufficient lowering of the blood-pressure to reduce the tension in the axons and dendrites of all neurons, not only of the cortex, but of the entire nervous system. Indeed, sleep does not mean repose of the cortex alone, but of the whole cerebro-spinal system. Goltz's dog, for instance, which lived eighteen months after its cerebrum had been removed, slept as do normal animals, even going through the preliminary circular movements peculiar to dogs.

This clearly indicates that the center which causes constriction of the vessels of the pituitary and thyroid lies below the brain, and, in the light of the evidence I have adduced, that it is to the neural lobes of the pituitary that we must ascribe this function. This organ, we have seen, sends fibers to the great-cell nucleus in the third ventricle, which nucleus,

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[17] *Cf.* this volume, p. 1125.

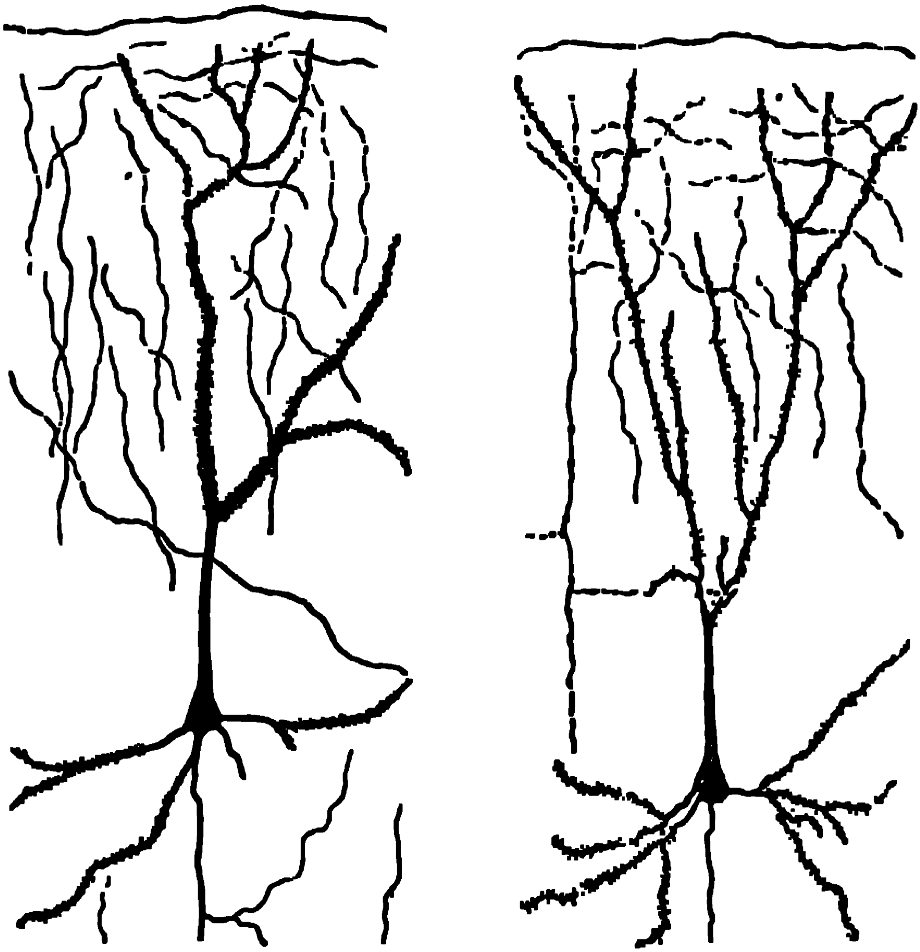

Fig. 1. *Fig. 2.*

BRAIN-CELLS OF MARMOT. Fig. 1, WHILE AWAKE; Fig. 2, WHILE ASLEEP. *(Querton.)*

Shows neuron dilated by adrenoxidase-laden plasma in Fig. 1, and the same cell depleted of plasma during sleep, in Fig. 2. (Sajous.)

in turn, sends fine fibers—those peculiar to the sympathetic system, as previously shown—to the medulla and cord, and to the anterior pituitary. Now Cyon found that the constrictor fibers distributed to the thyroidal arteries were derived from the cervical sympathetic; while Berkley specifies that the nervous supply of the anterior lobe is also of sympathetic origin. I have already submitted considerable evidence to the effect that the sympathetic was the vasoconstrictor of all arterioles. We are furnished here not only with additional testimony to this effect, but we are brought to realize that it is the sympathetic center in the posterior pituitary which, by inhibiting the circulation of the thyroid and of the anterior pituitary (including its test-organ and the adrenal center with which it is linked), causes sleep.

This evidence sustained by the data previously adduced seems to me to warrant the following conclusions: (1) *sleep is brought on by the sympathetic center;* (2) *by sending constrictor impulses to the arterioles of the anterior pituitary body (including its test-organ, which governs the adrenals) and also to the arterioles of the thyroid gland, this center lowers the metabolic activity of the body at large;* (3) *metabolism being also lessened in the cardiac and vascular muscular fibers, general vasodilation follows;* (4) *as this in turn entails augmentation of the blood circulating in the splanchnic area and other deep vessels, a corresponding volume of blood is withdrawn from the peripheral organs, including the cerebro-spinal system.* (5) *In the brain this lessened metabolic activity and diminution of adrenoxidase-laden plasma jointly provoke unconsciousness by inhibiting the functional activity of the neurons, which take part in all psychical processes;* (6) *in the spinal and peripheral nervous systems the same two conditions cause depression of sensibility, including that of the spinal motor cells which convert sensory impulses into motor stimuli.*

Hypnotism.—This condition is generally associated with sleep, but in the light of my views—to which only a brief allusion can be made here—it is a morbid process. Many theories have been advanced as to its nature; all, naturally, ascribing the phenomenon to some functional aberration of the cerebral cortex. That this does not account for the hypnotic state is indicated by the fact that, as shown by Verworn,[18] animals deprived of their hemispheres can be hypnotized. Landois[19] also writes: "Hens (also after removal of the cerebrum) assume a rigid position if an object be suddenly placed in front of the eye, or a straw be placed over the beak." . . . . This rigidity occurs in the human subject, and may be brought about in many ways which affect the lower animals similarly. This indicates that it is upon structures below the brain that the hypnogenic influence is exercised.

In the first volume[20] I referred to the posterior pituitary as the *sensorium commune*, and pointed out in the preceding[21] chapter, in connection with the meaning of "idiosyncrasy," that the sympathetic center stood foremost in this connection. Considerable evidence has already shown that this center governs the caliber of the arterioles, and that marked constriction inhibits function by reducing the volume of blood distributed to the peripheral capillaries. We have seen also that their dilation reduces the blood-supply. Evidence to the effect that such a condition prevails during hypnotic sleep is afforded by the pallor of the skin and mucous membranes, and the fact, noted plethysmographically by Walden,[22] that the arm and hand show a marked diminution in volume.

If we take into account the mechanical means capable of inducing hypnosis in man and animals: fixing intently a bright object, or revolving mirrors held a short distance from the face; a sudden flash, such as that of an electric spark; a stern command to go to sleep; the noise of a gong. etc., it becomes plain that a shock, strain of the ocular muscles entailing reflex sequences, etc., underlie the genesis of the hypnotic state. Its production by pressure upon hysterogenic zones also betokens reflex action through a center capable of influencing the vessels of the body at large, and, in the light of the foregoing evidence, those vessels which influence sleep. This indicates that the most sensitive center of the posterior pituitary, *the sympathetic center, is the source of the vasomotor impulses through which hypnotism is provoked,* and that the kindred states: *somnambulism, lethargy and catalepsy, are due to a corresponding process, likewise under the influence of the sympathetic center.*

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[18] Verworn: "Die sogen. Hypnose der Thiere," 1898.
[19] Landois: *Loc. cit.*, p. 780, 1905.
[20] *Cf.* vol. i, p. 596.
[21] *Cf.* vol. i, p. 596.
[22] Walden: Amer. Jour. of Physiol., vol. iv, p. 124, 1900.

EXCESS OF ADRENOXIDASE IN NERVOUS ELEMENTS AS A CAUSE OF PAIN.

Stewart,[23] in a brief review, writes: "Pain has been defined as 'the prayer of a nerve for pure blood.' The idea is not only true as poetry, but, with certain deductions and limitations, true as physiology. That is to say, pain, as a rule, is a sign that something has gone wrong with the bodily machinery; freedom from pain is the normal state of the healthy body. Physiologically, pain acts as a danger-signal; it points out the seat of the mischief." While the latter fact is true, and it is self-evident also that pain is an abnormal phenomenon, the connection between these two facts on the one hand, and the assertion that pain is "the prayer of a nerve for pure blood," is not clear. In truth, this conception, as I view it, is a most misleading one. Even in disorders such as gout, rheumatism, neuralgia, etc., in which the pain might be ascribed to the local action of noxious substances, the administration of an analgesic, morphine, for example, will subdue or even entirely remove the pain. It is evidently not the poison which causes suffering, since the analgesic certainly does not promote its destruction or removal. The pain must be subdued through some other mechanism.

Again, as stated by Howell,[24] "pain is probably the sense that is most widely distributed in the body. It is present throughout the skin, and under certain conditions may be aroused by stimulation of sensory nerves in the various visceral regions, and indeed in all of the membranes of the body. Our knowledge of the physiological properties of the end-organs and nerves mediating this sense is chiefly limited to the skin, and for cutaneous pain at least, the evidence, as stated above, is very strongly in favor of the view that there exists a special set of fibers which have a specific energy for pain. All recent observers agree that the pain sense has a punctiform distribution in the skin, the pain-points being even more numerous than the pressure-points." Briefly, pain is generated by a special neural mechanism possessing specific nerve-terminals, and occurs when, from some cause, these nerve-endings are stimulated. These causes, as is well known, are numerous, and when pain is due to traumatism, pressure, etc., it is readily accounted for by excitation of these sensory endings and the transmission of pain-impulses to the central nervous system.

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[23] Stewart: "Manual of Physiol.," fourth edition, p. 865, 1900.
[24] Howell: *Loc. cit.*, p. 262, 1906.

Here, however, we meet with an obstacle. How and by what organ are pain and its location perceived? Stewart states that "the precise mechanism of the localization is unknown. But," he adds, "we must *suppose* that each peripheral area is 'represented' in the brain, so that the afferent impulses from it affect particularly the related cerebral area. The brain therefore, so to speak, associates excitation of a given cerebral area with stimulation of the corresponding peripheral area, and thus not only recognizes the quality and quantity of the resultant sensation, but also localizes it." We have seen, however, that this supposition is not based upon a solid foundation. Goltz's dog, for instance,[25] which lived eighteen months after being deprived of its hemispheres, not only felt pain, but kept one of its paws, which had been hurt accidentally, raised from the ground until the injury had healed.

Referring to the same animal, Schäfer[26] writes: "It reacted promptly and consequentially to tactile impressions. When its skin was pinched it gave vent to its discomfort by snarling or barking just as a normal dog might do, and attempted to get away from the hand which was the source of discomfort, or, failing to do this, would turn round and bite at it, but in a clumsy manner and often without coming near it. If its feet were placed in cold water, they were quickly withdrawn." Again: "The rabbit, after removal of the hemispheres, in a few minutes sits up and begins to move about in an apparently normal manner. Its reflex excitability is increased. If the foot is pressed, it will kick and struggle violently." Striking in this connection is the behavior of the brainless frog. "If placed in a vessel of water the temperature of which is gradually raised," writes Ferrier,[27] "it will not quietly submit to be boiled like a frog which has only its *medulla* and *cord*, but will leap out as soon as the bath becomes uncomfortably hot."

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[25] *Cf.* this volume, p. 970.

[26] Schäfer: "T. B. of Physiol.," vol. ii, p. 702, 1900.

[27] Ferrier: "Functions of the Brain," second edition, p. 109, London, 1886.

These examples show clearly that it is not the brain which perceives pain or even its location, since, by limping on three legs, Goltz's brainless dog showed not only that it felt it, but that it located it in the raised limb. The location of the perceptive region is pointed out, moreover, by the behavior of the frog. Not any more than the hemispheres can the medulla oblongata or spinal cord be said to perceive pain, since the presence of these organs will not cause the frog to escape from the hot water; it is evidently a region *above* the medulla and *below* the brain. It is not due to the corpora striata or the optic thalami, for Schäfer, who quotes Ferrier, states that they "were included in the removal." This brings us once more to the only structure to which any such function can be attributed: the posterior pituitary. Indeed, in the sixteenth chapter[28] I submitted the conclusions, sustained by considerable evidence, that "the cortex is not the organ through which any of the cutaneous and internal sensations are perceived," and that "these sensations, which include pain, heat, cold, pressure (constituting touch), hunger, thirst, and the muscle and spatial senses, are perceived by and through the neural or posterior lobe of the pituitary."

Returning to the production of pain, we have seen that, aside from the traumatic or mechanical causes, the purity of the blood can hardly be granted the dominant position in the process that the poetical conception quoted above has earned for it. On the other hand, we have ample proof to the effect that an *excess* of blood in a given region can provoke suffering, and that its intensity varies with the degree of local congestion. Evidence to this effect need not be produced. It becomes a question whether *all pains* other than those due to traumatism are not due to local congestion. In neuralgia, for instance, even in the anæmic, pathological anatomy points to the presence of a neuritis either in the nerve itself or in the ganglion from which it originates. In *tic douloureux* such lesions are practically always found. The fact that, as I have shown, adrenoxidase circulates in nerves as it does elsewhere, accounts for these results. Again, the increase of pulsation in a painful area and the relief afforded by elevating the part in which it lies, point distinctly to a common cause—a fact further sustained by the relief afforded by morphine, whatever be the source of suffering.

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[28] *Cf.* this volume, p. 1097.

The so-called "toxic" form of pain might appear to constitute an exception, but analysis of the question soon shows that even here hyperæmia must be taken into account. In auto-intoxications of intestinal origin, we often have, as is well known, a rise of vascular tension, *i.e.*, a cause of congestion in nerves predisposed to neuritis, in aural structures previously diseased; in old pleural or peritoneal adhesions. In the pains due to mercury, lead, arsenic, alcohol, etc., the influence on vascular tension is also marked, some causing them by provoking active and others passive hyperæmia. The influence of increased vascular tension is well shown by the fact that, as shown by Richet, the sensibility to pain is reduced in idiots, imbeciles, and senile dements. Ioteyko[29] found the sensibility to heat decreased in melancholic women, and the initial sensibility to cold markedly increased. All these subjects bear the stigma of deficient peripheral circulatory activity.

Reducing the whole question to its simplest expression, a prominent fact asserts itself, viz., that *given the presence in any area of nerve-endings capable of transmitting pain impressions, congestion of that area from whatever cause, direct or indirect, will provoke pain.* As viewed from my standpoint, these minute sensory elements are the seat of metabolic processes in which adrenoxidase fulfills the function it does in all other cells: an increase of adrenoxidase here means increased metabolic activity and, therefore, increased acuity of the pain-impulses transmitted to the posterior pituitary.

THE SYMPATHETIC CENTER AS THE INTERMEDIARY THROUGH WHICH ANALGESICS PRODUCE THEIR EFFECTS.

In the light of the conclusions submitted in the two foregoing sections, any drug capable of reducing the blood circulating in the peripheral tissues, including the central nervous system, and of inhibiting metabolism in these tissues, should be capable of causing sleep and of arresting pain. Again, inasmuch as we have seen that it is the sympathetic center which governs the caliber of the arterioles, and, therefore, the blood supplied to these tissues, drugs capable of causing sleep and of subduing pain should do so through the intermediary of this center. That such is the case will be illustrated by the action of three of our main analgesics—morphine, antipyrin and acetanilid.

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[29] Ioteyko: Jour. de neurol., Oct. 5 to 20, 1905.

Both *opium* and *morphine* produce a temporary exhilaration, visions, etc., by augmenting the propulsive activity of the arterioles—a condition supplemented by a direct excitation of the vasomotor center and peripheral hyperæmia when *large* doses are taken. Under the influence of therapeutic doses this is soon succeeded by the typical action of the drug: constriction of the arterioles, and diminution of the blood supplied to capillaries and nervous elements in general, including those of the brain and spinal system and of any region which may be the seat of pain; this condition being brought about by the stimulating effect of the drug upon the sympathetic center. Both analgesia and sleep are produced by *therapeutic doses* because they influence this center only and the arterioles only, and the supply of arterial blood to the neurons, capillaries, etc., is reduced.

As produced by opium and morphine, sleep is caused indirectly, *i.e.*, artificially. We will see in the next chapter, in which the drugs that depress the adrenal and other centers are studied, that we have several agents (the bromides, chloral, etc.) which provoke sleep by a process approximating closely that of Nature.

Antipyrin and *acetanilid* arrest pain as does morphine, but an important feature deprives these analgesics of soporific properties; even in therapeutic doses they stimulate the vasomotor center and thereby keep the neurons of the central nervous system and the capillaries in general more or less engorged, thus defeating an essential condition of sleep. This blood, when the drug proves toxic either in small or large doses, may be detained in the peripheral capillaries through circulatory torpor and, becoming partly venous, cause cyanosis. Another feature illustrated by these drugs is that their action is prevented by section of the tissues immediately below the pituitary body (and, therefore, above the bulb), a procedure involving, therefore, division of the sympathetic fibers derived from the posterior pituitary.

OPIUM AND MORPHINE.

Physiological Action.—A small therapeutic dose of opium or morphine excites sufficiently the sympathetic center to cause slight contraction of the arterioles—that degree of constriction which, we have seen, provokes at each pulsation a reflex dilation of these vessels.[*] The alternation and exaggerated constriction and reflex dilation of the arterioles increases their propelling power, and an excess of blood is projected with each pulse-wave into all capillaries, including those of the cerebrospinal system.[*] Hence,[*] the period of mental vigor and excitement, visions, hallucinations sometimes witnessed, and which in subjects habituated to the use of the drug may attain the proportion of wild delirium.

In normal individuals, however, the mean caliber of the arterioles is, on the whole, reduced by a small dose, and the average volume of blood thrust into the capillaries being diminished,[*] a feeling of torpor, general and cerebral, is experienced, sometimes accompanied by a semiconscious condition or light sleep, a good part of which is taken up by dreams.

If the dose be large, the general and cerebro-spinal hyperæmia[*] manifests itself in a correspondingly more active way, and symptoms of actual cerebral congestion appear: the face is reddish or suffused and may even be cyanosed; the skin is warm and dry, the pulse strong and full.

The influence of opium and its preparations on the vascular system are generally recognized. Guinard[30] studied graphically the changes in the blood-pressure provoked by morphine in the higher mammals, the horse, ox, goat, sheep, pig and cat, and found that in all these animals the pressure was increased when the limits of therapeutic doses were not exceeded, and however introduced. The rise was always very marked. Gscheidlen[31] also observed primary vasoconstriction; having injected morphine in animals, he saw the *arterioles* of the mesentery contract. The primary rise of blood-pressure occurs under these conditions in the arteries behind the arterioles, owing to the obstruction which the latter present to the blood-stream. The venous engorgement which this should entail is likewise present. Picard[32] observed, after he had injected from 0.06 to 0.08 gms. (1 grain to $1^{1}/_{2}$ grains) in a dog and opened a vein in an exposed submaxillary gland, that the blood-flow was increased, notwithstanding division of the chorda tympani. This shows that the gland's secretory nerve, which normally causes the increased blood-flow when stimulated, played no part in the production of this phenomenon under the influence of morphine, and that it was due to the general vasoconstriction which this drug provoked. Cushny[33] states that the "blood-pressure remains high" under the influence of morphine.

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[*] *Author's conclusion.*

[30] Guinard: C. r. de la Soc. de biol., 10 série, vol. ii, pp. 551, 572, 1895.

[31] Gscheidlen: Untersuch. aus dem physiol. Lab. zu Würzburg, 2ter Theil, 1869.

[32] Picard: C. r. de l'Acad. des Sci., May 6, 1878.

The influence of partial contraction of the arterioles may be illustrated by the action of morphine upon certain animals. We have seen that Guinard observed powerful vasoconstriction in the horse, ox, goat, sheep, pig and cat. In all these animals morphine causes excitement, but not narcosis. In the dog, rabbit, guinea-pig, white rat and mouse, on the other hand, he also observed general vasoconstriction, but with narcosis. Yet, this does not mean that the horse cannot be made to sleep by morphine: Harley,[34] for instance, found that large doses, 12 grains (0.8 gm.), produced very great excitement in this animal, not only cerebral, but general, as indicated by frothing at the mouth, muscular tremors, great restlessness, etc. In another experiment he gave a horse 36 grains (2.4 gms.) of morphine acetate. This powerful dose caused the animal to sleep three hours, but on awakening he passed through the stage of excitement, and this continued some seven hours. Again, in the mouse, which is readily put to sleep by adequate doses, Harley caused tonic spasm of the trunk, abnormal sensitiveness to sounds, etc., without narcosis by giving small doses. This clearly shows that the *caliber* of the vessel determines the character of the cerebral phenomena provoked, *i.e.*, *excitement* when an inordinate quantity of blood is admitted to the cellular elements; *sleep* when a smaller quantity than usual reaches them, owing to marked constriction of the arterioles. Manquat[35] deems it remarkable that the more intellectual Europeans should show more particularly the narcotic effects of the drug, while others, the Malays for instance, are rendered wildly delirious by it. This assumes a normal aspect when the sympathetic center is regarded as the intermediary of the drug's action—that of the European being more sensitive, the arterioles are sufficiently constricted to induce sleep; in the less sensitive races, they remain sufficiently patent to admit an unusual amount of blood in the brain, *i.e.*, to induce excitement.

ACTION AS ANALGESIC.—Opium and morphine reduce or arrest pain when the arterioles are sufficiently constricted under its influence to diminish the volume of blood supplied to the painful area.* The sensory end-organs of this area, previously overstimulated through local hyperæmia, are thus freed of the excess of blood to which the pain is due.* This process is further enhanced by the fact that the constriction of the arterioles tends to produce capillary stasis; the blood being reduced by the tissues as usual, it tends to become venous, and thus to reduce sensibility in the sensory terminals it supplies.*

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* *Author's conclusion.*

[33] Cushny: *Loc. cit.*, fourth edition, p. 212, 1906.

[34] Harley: Cited by Wood: *Loc. cit.*, eleventh edition, p. 124, 1890.

[35] Manquat: *Loc. cit.*, vol. ii, p. 437, 1903.

The general constriction of the arterioles, by slowing the circulation and diminishing the volume of blood supplied to all tissues, must necessarily lower the rate of metabolism. E. T. Reichert[36] found in twelve experiments in dogs that general metabolism, as determined by heat-production, falls on an average 26 per cent. below the normal during the first hour, 62 per cent. during the second hour, and 40 per cent. during the third hour, with an average temperature fall in the rectum of 1.76° C. (3.17° F.). This harmonizes with the observation of Boeck and Bauer[37] and Chittenden and Cummins,[38] that the elimination of carbon dioxide is reduced during the narcotism induced by the drug. Guinard ascertained that both the intake of oxygen and the output of carbon dioxide were reduced. Wood and Cerna[39] also found experimentally, as did Guinard, that morphine acted as a depressant of the respiration. Heger,[40] moreover, showed that the slowing of the respiration caused by the drug was closely related with the diminution in the respiratory exchange, the animal consuming less oxygen and producing much less carbon dioxide than normally.

That reduction of the blood supplied to the skin, and other structures containing end-organs, should, under these conditions (especially in view of the capillary stasis which it entails), diminish their relative sensibility is self-evident. Moreover, experimental testimony points in the same direction. Cushny,[41] for instance, referring to several observers who have studied the relative sensibility of the skin by measuring the smallest distance at which two points could be distinctly recognized, states that "in every case it was found that the ability to do this was lessened by morphine." The analgesia produced is not due to a direct action of the drug upon the sensory organs themselves, for Gscheidlen found that when applied locally to a sensory nerve during strychnine-poisoning, morphine increased its excitability and prolonged it. Manquat[42] states that while "the contact of morphine irritates mucous membranes and skin deprived of its epidermis, causing an unpleasant pricking sensation, this is soon replaced by lowering of the sensibility." This represents about the only tangible fact in favor of the prevailing view that morphine produces analgesia and sleep by acting directly upon the cerebral and other nervous elements after stimulating them. But we cannot logically compare the local effects of a solution of morphine of 1 to 400,000—such as a 1/4 grain (0.016 gm.) dose makes with the thirteen pounds of blood in the body—with those of the alkaloid itself applied to mucous membranes or to denuded tissues. Even here, proof of the fallaciousness of the present conception asserts itself. Morphine is a reducing agent, and, as shown by Landsberg and Marmé, it is converted in the tissues into oxydimorphine. It is, therefore, because it deprives the tissues to which it is directly applied *of their oxygen* that it obtunds sensibility. It does so, in other words, merely by inhibiting metabolism in those tissues precisely as would any other equally active reducing agent, and not *as* morphine. But this proves also that diminished tissue-oxidation is the underlying cause of analgesia, and morphine, by so stimulating the sympathetic center as to reduce the blood-supply in a congested and therefore overstimulated structure, does nothing else.

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[36] E. T. Reichert: Phila. Med. Jour., Mar. 9, 1901.

[37] Boeck and Bauer: Zeit. f. Biol., Bd. x, S. 336, 1874.

[38] Chittenden and Cummins: Studies from the Lab. of Physiol. Chem. of Yale Univ., vol. ii, p. 200, 1887.

[39] Wood and Cerna: Jour. of Physiol., vol. xiii, p. 870, 1892.

[40] Heger: Bull. de l'Acad. de med. de Belg., 4 série, T. xiv, p. 137, 1900.

[41] Cushny: *Loc. cit.*, fourth edition, p. 211, 1906.

[42] Manquat: *Loc. cit.*, vol. ii, p. 437, 1903.

ACTION AS HYPNOTIC.—Sleep is also induced by morphine because it provokes general constriction of the arterioles.* By thus reducing the blood supply to the brain and spinal cord, it lowers their functional activity, as it does that of other organs.* Morphine thus incites artificially a condition very similar to normal sleep, since the latter is likewise due to diminished irritability of the cerebro-spinal system.* Morphine sleep differs from normal sleep only in that the irritability of the nerve-cells is reduced by a diminution of the volume of blood, and, therefore, of adrenoxidase supplied to them, while in normal sleep the blood's oxygenizing properties are reduced through a diminution of the proportion of adrenoxidase in the blood, the result in turn of a physiological depression of the adrenal center.*

That the sleep induced by morphine is due to diminution of the blood circulating in the brain has been determined experimentally. Thus Kauffmann[43] observed "slowing of the capillary circulation with stasis," while Stcherbach[44] found that there was "diminution of the blood flowing to the brain"—a normal consequence of contracted terminal arterioles. This evidently applies to the entire circulation, for Guinard also found a diminution in the speed of the carotid current, which, by diminishing the blood supplied to various organs, checks the various secretions of the body, *i.e.*, *inhibits* their functions. Both Nothnagel[45] and Isaac Ott[46] found that opium checked peristalsis in animals as it is known to do in man. On the whole, the changes of vascular caliber which endow morphine with its analgesic properties are also those which render it a soporific. The only difference between the two phenomena is that a larger dose is required to cause sleep *besides* analgesia, than it does to obtain analgesia alone. Thus, as stated by Cushny,[47] "in man, it is often found that comparatively small quantities are sufficient to deaden or even entirely remove the pain of disease without rendering the patient unconscious." This is simply because pain is caused by so slight an exacerbation of local metabolic activity that a slight vasoconstriction will counteract it, while the production of sleep requires a greater degree of vasoconstriction to induce the state of "diminished irritability of the nervous system" which, according to Landois,[48] exists during sleep.

The *after-effects* of morphine are due to a depression of the sympathetic center which lasts in proportion as the recuperative power of the center is marked.* Usually this is sufficiently great to prevent appreciable untoward effects after small doses; otherwise, even these may cause: lassitude, owing to the loss of tone of the arterioles in the skeletal muscles; nausea or vomiting, because of a similar condition in the gastric mucous membrane and muscles; and headache, owing to cerebral hyperæmia.[*]

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* *Author's conclusion.*

[43] Kauffmann: Cited by Guinard: *Loc. cit.*

[44] Stcherbach: *Ibid.*

[45] Nothnagel: Virchow's Archiv, H. 1, S. 1, 1882.

[46] Isaac Ott: N. Y. Med. Jour., Aug. 18, 1883.

[47] Cushny: *Loc. cit.*, fourth edition, p. 210, 1906.

[48] Landois: *Loc. cit.*, p. 778, 1905.

In neurasthenic individuals, especially women, the morbid effects of this secondary vasodilation may assume alarming proportions. The lassitude lapses into prostration with a low peripheral temperature, due to depletion of the cutaneous capillaries.[*] Vertigo and fainting replace the headache when this occurs, both due to inadequate supply of blood to the brain.[*] Nausea and vomiting are usually very marked in these cases, the effusion of blood-fluids into the stomach, and the dilation of this viscus because of the relaxation of its muscles, being correspondingly great. The heart's action is also morbidly influenced by the relaxation of its nutrient arterioles[*] and its action becomes feeble. As a result of this cardiac adynamia, the blood is not propelled with adequate vigor into the lungs, causing dyspnœa, nor into the vascular system. A vicious circle is thus established[*] which may culminate in syncope and death.

The explanations given in the text are self-evident. The corresponding effects in animals are very marked. Wood[**] states that "after awaking, the dog shows unmistakable signs of nervous and psychical depression. In walking, the hind legs are dragged, as though semiparalyzed; the eyes are haggard; the naturally brave animal cowers in a corner or seeks to hide himself, no longer recognizing his master. After smaller doses, the effects are proportionally less intense. It has been shown by Harley," says the same author, "that in some dogs, precisely as in some people, morphine fails to exert its usual hypnotic action, but produces great depression, as evinced by faintness, prolonged nausea and retching, interrupted only by intervals of dreamy, delirious somnolency."

Morphinism.—In this condition the morbid phenomena witnessed are due to a condition differing from the foregoing only in that the sympathetic center, overtaxed by the continuous use of the drug, finally becomes unable to preserve the tone of the arterioles throughout the organism, unless stimulated by steadily increasing doses.[*] This entails the development of *morphinomania,* since the craving for the drug is prompted by the pleasurable sensation that relief of the suffering provoked by general vasodilation procures.

The symptoms betray plainly the loss of vascular tone:[*] weak and sometimes irregular pulse and heart-beat; light sleep, disturbed by unpleasant dreams or distressing insomnia, both due to passive hyperæmia of the cerebral capillaries and cells; hallucinations, day-dreams, and occasionally delirium, due to the same cause; sensory disorders, hyperæsthesia, formication, etc., due to fluctuations of vascular tension; anæsthesia when, on the other hand, the central trunks are widely dilated at the expense of the peripheral vessels and, therefore, of those which supply the cutaneous sensory endings; diminution of the reflexes and disorders of locomotion from the same cause; atonic dyspepsia, nausea, vomiting, diarrhœa—all due to dilation of the gastro-intestinal vessels, and the resulting relaxation of muscles and mucosa.

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[*] *Author's conclusion.*

[**] Wood: *Loc. cit.*, thirteenth edition, p. 128, 1906.

Complications incident upon the loss of vascular tone soon appear.* Pustular and urticarial eruptions betoken the inadequate conversion of toxic wastes,* both in the liver and the blood—a morbid factor for which simple vasodilation does not account. The lowered oxygenation of the peripheral tissues may also give rise to abscesses, gangrene, progressive emaciation, and muscular atrophy and loss of sexual powers. As the case progresses, the circulation in both lobes of the pituitary body also becomes inadequate* and general collapse occurs. The test-organ and adrenal center are the first to feel the effects of this condition, owing to the great vascularity of the anterior lobe; as this organ constitutes, with the adrenals, the thermogenic mechanism, inhibition of its functions entails a corresponding decline of oxygenation and metabolism throughout the entire organism,* a condition soon followed by dissolution.

The familiar clinical facts recited, the exaltation produced by the drug followed by marked depression, asserts itself also experimentally. Thus Kraepelin,[80] in a study of the action of morphine upon the brain, found that it caused first marked excitation of the sensory functions and a subsequent marked and rapid depression of the same. He noted, moreover, that it produced a decided and persistent paralysis of the motor functions. The great depression of the adrenal system, which may occur at any time, is shown by the fact that bronzing is sometimes witnessed. Thus, in a case successfully treated by Sollier,[81] the skin of the entire body had acquired the Addisonian hue. That the adrenal center—the thermogenic center, in the light of my views—is depressed, is indicated not only by the marked fall of temperature, but also by the experiments of Reichert,[82] which showed that the hypothermia caused by a toxic dose of morphine was due to "depression of the thermogenic centers in the caudate nucleus" and to the resulting heat-production. Confirmatory also in this connection is the fact that the drugs which have been found most beneficial in morphinism are those which improve the vascular tone or which stimulate the adrenal center. Norman Kerr,[53] for example, recommends digitalis and strophanthus, which combine both properties. Hunter Wells,[54] in fact, found adrenalin strikingly effective in the treatment of a large number of cases in Korea.

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* *Author's conclusion.*

[80] Kraepelin: Riforma medica, July 11, 1892.

[81] Sollier: Le progrès médical, May 12, 1900.

[82] Reichert: Phila. Med. Jour., Mar. 9, 1901; Univ. of Penna. Med. Bull., Nov., 1903.

Acute Poisoning.—All the phenomena enumerated in the foregoing pages occur in more or less rapid succession when a large dose of morphine is taken. The sympathetic center bears the brunt of the action of the poison, but the vasomotor center is also excited at first, so that a large quantity of blood is forced into the capillaries.[*] So marked is the general vasoconstriction—both arteries and arterioles—in the first stage, that all the blood is practically transferred to the capillaries and veins.[*] The circulation being thus greatly hampered and slowed, the arterial blood is rapidly reduced, *i.e.*, deprived of its oxygen, by the surrounding tissues, and becomes dark and even absolutely venous in the capillaries.[*] Hence[*] the suffused, bloated and deeply cyanosed face and the labored and sometimes stertorous respiration, the contracted pupil, and the slow and forcible action of the heart, mainly due to the marked resistance of the blood-column.

The sleep of a toxic dose of opium or morphine differs from that produced by a therapeutic dose of these agents in that it is stuporous, and due to the venous condition of the blood circulating in the cerebro-spinal system.[*] It occurs soon after the ingestion of the poison, and deepens to a condition from which the patient can only be roused with the greatest difficulty.

The relative arterial constriction is so great that the accumulation of blood in the veins can sometimes be discerned after death. Thus J. Ewing[55] found in a case of acute poisoning that "there was extreme œdema of the lungs, and marked *venous* congestion of all viscera." The œdema further indicates the extreme tension to which the vessels submitted—serum having been evidently forced through capillary walls. Both Kauffmann and Guinard found, we have seen, that the blood-stream was slowed, owing to this vasoconstriction.

The case may, under appropriate treatment, recede at this stage, the morbid phenomena disappearing gradually, or it may proceed on its lethal course to the stage of collapse.

Collapse is due here to a combination of two factors: the extreme general vasoconstriction, due to direct irritation of the vasomotor center, and, as a result of the interference with the circulation, a venous condition of the blood.* This venous blood is the cause of the lethal trend, however, since the lack of oxygen first depresses, then paralyzes, the test-organ, the adrenal center, and the adrenals themselves.* The adrenal center being both the respiratory and thermogenic center,* death is caused by respiratory failure.

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[*] *Author's conclusion.*

[53] Norman Kerr: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. v, p. 37, 1900.

[54] Hunter Wells: W. Va. Med. Jour., Dec., 1906.

[55] J. Ewing: Arch. of Neurol. and Psycho-Path., vol. i, p. 263, 1898.

The symptoms observed are quite in keeping with this morbid process: the respirations grow steadily weaker, slower, shallower, and more distant. The skin, being supplied with blood deficient in oxyhæmoglobin, is at once pale and cyanotic. The heart and pulse become gradually weaker, smaller, and irregular, until, shortly after cessation of respiration, they can no longer be discerned.

Dott and Stockmann[26] found that after *large* doses morphine lowered the vascular pressure, owing, they thought, to "depression of the respiratory center." Reichert[27] also published records which show that "morphine is not only a *powerful thermodepressant*, but that it has also, coupled with this action, one of some potency of the opposite character, as is indicated by the fact that the profound rapid fall of temperature may be preceded by a rise, or may be checked by a secondary rise, or both." The interpretation I submit in the general text accounts for these antagonistic phenomena: the rise of temperature occurs when the adrenal system has the upper hand; and the fall when the venous blood is depressing its action. Now, Reichert[28] pointed out a very important fact in this connection, viz., that cocaine antagonized morphine-poisoning, and clinical observations have sustained his conclusion. On the other hand, I have called attention, in the article on cocaine, to the fact that this alkaloid exceeded others greatly in power as a stimulant of the test-organ and adrenal center. The value of cocaine as a direct antagonist of morphine is thus accounted for: by powerfully exciting the adrenal center it sustains its functions notwithstanding the venous condition of the blood, and, by thus enforcing a rapid production of adrenal secretion, increases in proportion the volume of adrenoxidase in the blood. This affords the precise weapon needed to save the patient's life, since by endowing his blood with oxygenizing properties, its venous quality, the deadly feature of the process, is simultaneously eliminated.

The *treatment of opium and morphine poisoning* is described in a special section at the end of this volume.

Therapeutics.—Opium and morphine have not been superseded by any of the more modern agents for the relief of pain. This cannot be said of their use in *insomnia*, for we have better hypnotics, though none can replace morphine when pain and insomnia are present simultaneously. The manner in which opium and morphine produce both these effects (according to my interpretation) suggests, however, a number of *contraindications:* in disorders of the brain, cerebral congestion, meningitis, mental excitement, delirium, etc., the use of large doses of morphine, by causing cerebral hyperæmia, tends to aggravate the symptoms. Morphine is sometimes used in tetanus, epilepsy, eclampsia, etc., but the convulsions being due to an accumulation of toxic wastes, the slowing of the capillary circulation and the venous condition of the blood tend to inhibit catabolism and thus to increase the proportion of these wastes,* the result being, in the end, an augmentation of the spasms. Their use in fevers is open to the same objection, since the febrile process is a protective one, carried out by an excess of auto-antitoxin in the blood.* To prevent the access of this blood to the capillaries of the liver and skin, where the pathogenic organisms and toxins are mainly destroyed, by provoking constriction of the arterioles is to defeat Nature's protective efforts. In intestinal disorders, the same protective function is carried out in a different way, *i.e.*, by the copious secretion of the constitutents of auto-antitoxin into the intestinal fluids, peristalsis being likewise enhanced to insure elimination of the offending materials.* Opium and morphine, by causing undue constriction of the intestinal arterioles, arrest both the antitoxic flushing and peristalsis.* This applies as well to the copious expectoration which serves to eliminate pathogenic materials and detritus from the respiratory tract. All these contraindications are sustained by clinical observation. To this may be added the marked susceptibility of very young children, of debilitated individuals of all kinds to its effects, and the danger of morphinism—which precludes its prolonged use.

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* *Author's conclusion.*

[26] Dott and Stockmann: Proceedings of the Royal Soc. of Edinburgh, 1891.

[27] Reichert: Univ. of Penna. Med. Bull., Nov., 1903.

[28] Reichert: Therap. Gaz., July, Aug., 1902.

There are many conditions, however, in which its value is firmly established. After the vomiting and purging of *cholera morbus* have insured elimination of the toxic materials, morphine checks the severe abdominal pain by causing constriction of the intestinal arterioles, thus inhibiting the excessive peristaltic action and the intestinal flux.* A similar action on the intestines promptly relieves the marked suffering of *lead colic.* In *hæmorrhage,* and especially the intestinal hæmorrhage due to *intestinal perforation,* morphine promptly stops the blood-flow by the same process,* since it is through the arterioles that the bleeding area is supplied with blood. By inhibiting the peristaltic movements, moreover, it tends materially to prevent recurrence. In *asthma* of nervous origin, in which the face is pale—a condition due to a marked lowering of the blood-pressure—morphine will often arrest a paroxysm by causing a rise of the latter and thus increasing the volume of blood exposed to the air in the pulmonary alveoli.* In *diabetes,* morphine proves useful by depressing the excessive functional activity of the adrenal center, thus reducing the proportion of adrenal secretion, *i.e.,* of adrenoxidase, in the blood, a frequent cause of this disease.

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* *Author's conclusion.*

DRUGS WHICH RESEMBLE MORPHINE IN THEIR PHYSIOLOGICAL ACTION.

Codeine differs from morphine only in that it is considerably less active and, therefore, less poisonous. Such being the case, the stage of stimulation is more marked, and the propulsive activity of the arterioles is kept up much longer than under morphine,* the constriction of the arterioles, which endows the latter with its analgesic and hypnotic properties, coming on much later.* Hence the value of codeine in *irritative coughs, mild bronchitis,* etc., since by increasing the supply of blood to the bronchi, it enhances (when given in small doses) the activity of the local curative process. In large doses, its action resembles that of morphine, but it does not as actively excite the sympathetic center. All the properties due to abnormal constriction of the arterioles* are therefore less evident: the sleep produced is light and not restful; the effect on pain is also slight and fugacious; it does not inhibit peristalsis materially, nor cause constipation as readily as does morphine. For reasons submitted under "Tuberculosis" I do not advocate the use of opiates in the treatment of cough.

Heroin acts much as does codeine, and its value in *irritative coughs* is also due to the fact that it increases the propulsive activity of the arterioles and thus increases the volume of arterial blood circulating in the bronchial capillaries in a given time.*

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* *Author's conclusion.*

Salicylic Acid; the Salicylates.—These agents act much as do opium and morphine, but their action upon the sympathetic center is less violent.* In small therapeutic doses they cause hyperconstriction of the arterioles and arrest pain by reducing the volume of blood supplied to all tissues, including the painful area.* Simultaneously, and unlike the coal-tar products, they stimulate actively the test-organ, and through it the adrenal mechanism, thus augmenting the blood's asset in auto-antitoxin.* Hence the fact that, besides acting as analgesics in *rheumatism* and *gout*, they prove curative, since they not only decrease the volume of blood circulating in the nerves of the painful regions,* but they also promote catabolism and the destruction of the pathogenic elements.

In large doses, salicylic acid and the salicylates increase the propulsive activity of the arterioles, and thus cause sufficient hyperæmia of the central nervous system* to evoke symptoms similar to those of cinchonism, tinnitus, headache, etc., and even hallucinations and delirium. Such doses are always dangerous, since at any moment they may cause such a marked reduction of the mean caliber of all arterioles that the cardiac muscle is inadequately supplied with blood, and thus rendered unable to carry on its functions.

ANTIPYRIN.

Physiological Action.—In some cases any dose of antipyrin, small or large, causes cutaneous hyperæmia. The skin becomes flushed, unusually warm and hyperæsthetic, and the flow of urine is increased and the reflexes are overactive. This is due to a temporary excitation by the drug of the vasomotor center.* All the arteries of the body being thus caused to contract, an unusual volume of arterial blood is driven into the arterioles and capillaries, including those of the skin.*

In the average case, however, this preliminary stage is of too short duration to be noticed.* Nevertheless, the cutaneous engorgement occurs, and may be marked even under the influence of small doses.

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* *Author's conclusion.*

Familiar symptoms point clearly to engorgement of the peripheral capillaries. Thus, H. Blakeney[59] observed a case in which there appeared, when 10 grains (0.64 gm.) had been "scarcely swallowed," a burning sensation in the mouth and throat and "extraordinarily rapid swelling" of the lips and cheeks, which quickly spread. Cerna and Carter[60] found that both small and large doses raised the arterial pressure. Casimir[61] also noted that the arterial pressure caused by this drug was accompanied by contraction of the internal vessels, including those of the kidney. The presence of excessive cutaneous hyperæmia is also shown by the marked exaltation of reflex sensibility observed, after the injection of moderate doses, by Blumenau,[62] Arduin, Demme, Simon and Hoch,[63] and other investigators. Tactile sensibility was raised to such a degree in Blumenau's animals (cat and frog) that the least touch or noise caused general convulsions. Shoemaker[64] also states that in animals "it occasions epileptiform and tetanic convulsions."

Halliday[65] found that such slight stimulation as blowing the breath gently on the surface of the animal's body greatly intensified its reflex movements and caused convulsions. Sudzilovski[66] noted increased urination in frogs, rabbits and dogs.

All these phenomena are evidently of nervous origin, for, while Bouchard[67] observed that moderate doses of antipyrin caused muscular rigidity, Blumenau found that division of the sciatic and crural nerves caused the muscles supplied by these nerves to preserve their normal state when antipyrin was given while all others were rigid.

"Notwithstanding the elevation of the blood-pressure," writes Manquat,[68] "vasodilation is observed even after small doses." Peripheral vasodilation after small doses was noted by Coppola,[69] Querrolo,[70] Maragliano[71] and others. This vasodilation can be seen in the ear of rabbits, according to Casimir,[72] while Maragliano and Querrolo found plethysmographically that the immersed arm was increased in size by antipyrin, showing that its peripheral vessels were dilated. Pisemski[73] noted at the autopsy of dogs poisoned by daily doses of 15 to 45 grains (1 to 3 gm.) "intense engorgement of the brain and meninges with a serous exudate into the cerebral ventricles."

The effects of this hyperæmia are soon masked, however, by those of the characteristic action of the drug. viz., excitation of the sympathetic center.* As a result, the sympathetic vasoconstrictors distributed to the arterioles cause abnormal constriction of these vessels, and the blood supplied by them to the capillaries is diminished in proportion.*

We have seen that Cyon and Masay caused general vasoconstriction by stimulating directly the pituitary body and that the investiga-

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* *Author's conclusion.*

[59] H. Blakeney: Brit. Med. Jour., July 8, 1899.

[60] Cerna and Carter: Notes on New Remedies, Sept., 1892.

[61] Casimir: Thèse de Lyons, 1896.

[62] Blumenau: St. Petersb. med. Woch., Bd. xii, S. 439, 1887.

[63] Simon and Hoch: Johns Hopkins Hosp. Bull., Apr., 1890.

[64] Shoemaker: "Materia Medica and Therap.," sixth edition, p. 717, 1908.

[65] Halliday: Montreal Med. Jour., July, 1897.

[66] Sudzilovski: Vratch. Nov. 24, 1901.

[67] Bouchard: C. r. de la Soc. de biol., 8 série, vol. 1, p. 729, 1884.

[68] Manquat: *Loc. cit.*, vol. ii, p. 571, 1900.

[69] Coppola: Riv. di Chem. Med. e Farmac, vol. ii, fasc. ix r x, p. 448, 1884.

[70] Querrolo: Cited by Deveaux-Armand: Thèse de Nancy, 1885.

[71] Maragliano: Gaz. degli Osped., 1882.

[72] Casimir: *Loc. cit.*

[73] Pisemski: St. Petersb. Inaug.-Dissert., p. 48, 1887.

tions of Ramon y Cajal, Andriesen, Gentès and others have shown that the pituitary body was connected with the central gray substance of the base of the brain and the bulb by nerve paths. The latter include, as previously shown, numerous sympathetic fibers. Now, when these are severed between the pituitary body and the bulb, that is to say, *above* the latter, antipyrin and other antipyretics are *no longer active*. This important fact was established by Sawadowski,[74] though he was unaware of the functions of the pituitary body. He transected the basal ganglia, "the cut being made through the thalami optici or the posterior surface of the corpora striata." We have seen that the sympathetic fibers from the pituitary cross the surface of the optic thalami; transection of the latter, therefore, or behind the corpora striata, inevitably severed these fibers, preventing thereby the general vasoconstriction. While emphasizing the fact that the action of antipyrin was *central*, he states that in thirty-eight more or less successful experiments "neither the injection of putrid substances, nor of antipyrin into a vein were able to induce any change in the temperature course." In other words, the putrid substance could no longer raise the temperature as it did in normal animals, while antipyrin could no longer raise and subsequently lower it, as it does in normal and febrile animals in which the nerve-paths of the base of the brain are normal.

Sawadowski refers to the possibility of an action of antipyrin "through the agency of the vasomotor system or by diminution of heat production," but he states that "this cannot be determined." He refers to his investigations as having established "that diminution of the *internal* temperature went hand in hand with increase in the *skin* temperature in consequence of dilatation of the vessels of the skin, which fact had already been indicated by Maragliano and his school." This obviously harmonizes with the conclusion to the same effect I have submitted in the foregoing paragraphs.

ACTION AS ANTIPYRETIC.—It is by producing excessive constriction of the arterioles that it provokes through the sympathetic center, that antipyrin reduces the peripheral temperature.* The caliber of the arterioles being materially reduced, the circulation of the blood in the capillaries is correspondingly slowed, and, being exposed unusually long to the reducing action of the tissues, it becomes more or less venous soon after penetrating the capillaries.* The surface temperature is lowered in proportion. This action is enhanced by a similar constriction of the arterioles of the anterior pituitary.* The circulation in the organ being reduced, the functions of the adrenal center, and therefore of the adrenals likewise, are depressed and less adrenoxidase is formed.* Blood poor in oxygen now constituting the torpid streams circulating in the capillaries, and being reduced as usual by the tissues, it becomes venous unusually soon.* This is so marked in some cases, that cyanosis is produced. Sweating, due to relaxation of the sweat-glands similar to that observed in moribunds,* depression, cooling of the surface, shivering, and lowering of the peripheral temperature in febrile subjects, all occur as a result of this morbid process.*

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* *Author's conclusion.*

[74] Sawadowski: Centralbl. f. d. med. Wissen., Bd. xxvi, S. 145, 161, 1888.

Many well-known clinicians, including Robin, have protested against the use of antipyrin to reduce fever. Bardet,[75] over ten years ago, referring to this drug, laid stress on the fact that "it is always dangerous for the organism to interfere with oxidation processes." Martinet,[76] in a more recent research, found that antipyrin interfered with nutrition and oxidation. Robin[77] has likewise shown that antipyrin reduces oxidation and that large doses of the drug reduce the elimination of urea 21 to 33 per cent. Wood[78] states that the original studies of Umbach,[79] "who found that large doses of antipyrin very markedly decrease the elimination of urea," have been "abundantly confirmed," and refers to the investigations of Wiczowski, Walter, Müller, Robin, Jacubovitsch and Tausk. Along with Wood, Reichert and Hare,[80] he had experimentally ascertained—a fact subsequently confirmed by Destrée,[81] Cerna and Carter[82] and others—that in febrile animals antipyrin markedly decreased the heat-production.

The cyanosis occasionally witnessed is at times very marked. In an instance reported by McCaully Hayes,[83] for example, the patient's face, within a quarter of an hour after taking 10 grains (0.64 gm.) "was cyanosed, his nose swollen and blue, and his eyes almost closed from swelling of the eyelids," the skin being "*cold* and clammy." In a case observed by E. Webster,[84] the "lips and general aspect were decidedly cyanotic," though the mixture administered had only contained 5 grains. The face was swollen, especially about the eyes—"so much so as to prevent any possibility of opening them." The temperature in the axilla was only 97° F. (36.1° C.).

Cyanosis has been ascribed to a transformation of oxyhæmoglobin into methæmoglobin by Lépine[85] and Hénocque.[86] Yet, Vierordt[87] thirty years ago, found that rubber rings left from 40 seconds to 5 minutes at the base of phalanges, caused the two spectroscopical bands of oxyhæmoglobin of the blood in the latter to be replaced by a single band indicative of *reduced* hæmoglobin as it occurs in venous blood. Halliday[88] also examined spectroscopically blood taken from the cyanosed lips of frogs and rabbits, both before and after death from antipyrin poisoning, and found that "the spectrum of methæmoglobin was certainly not present." Others have recorded similar observations. Cyanosis here, therefore, is evidently not due to methæmoglobin, but to the familiar cause of this phenomenon, *i.e.*, the accumulation in the blood of the capillaries of carbon dioxide.*

Action as an Analgesic.—Antipyrin relieves pain by reducing directly the sensitiveness of the peripheral sense-organs.* The process is identical to that provoked by the drug in the reduction of fever.* Small doses suffice to irritate the sympathetic center adequately for this purpose, and the resulting constriction of the arterioles reduces the quantity of blood supplied to all peripheral organs. Pain being due to an excess of arterial blood in sensory nerves or their endings, it is not only relieved from this cause, but also by the fact that what blood is supplied to the sensory elements is poor in oxygen.*

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* *Author's conclusion.*

[75] Bardet: Bull. et mem. Soc. de therap., p. 158, 1896.

[76] Martinet: La Presse méd., vol. xi, p. 788, 1904.

[77] Robin: Bull. de l'Acad. de méd., 2 série, vol. xviii, p. 701, 1887.

[78] Wood: *Loc. cit.*, thirteenth edition, p. 606, 1906.

[79] Umbach: Arch. d. exp. Path. u. Pharm., Bd. xxi, S. 161, 1886.

[80] Wood, Reichert and Hare: Therap. Gaz., Sept. 15, 1886.

[81] Destrée: Jour. de méd. de chir., et de pharm., vol. lxxxvi, p. 417, 1888.

[82] Cerna and Carter: *Loc. cit.*

[83] McCaully Hayes: Brit. Med. Jour., Feb. 1, 1896.

[84] Webster: Lancet, Jan. 30, 1897.

[85] Lépine: Lyon méd., vol. lii, p. 501, 1886.

[86] Hénocque: La semaine méd., vol. xv, p. 368, 1895.

[87] Vierordt: Zeit. f. Biol., Bd. xi, S. 187, 1875.

[88] Halliday: *Loc. cit.*

The investigations of Coppola, Querrolo and Maragliano[89] have shown that although the pressure is raised, peripheral vasodilation is observed even after small doses. This shows that small doses can evoke the typical effects of the drug. Simon and Hoch[90] found, moreover, that even in the earlier stages of the convulsive period, operations could be performed upon animals without anæsthetic. The general anæsthesia caused by the drug here is but an exaggerated expression of its effect as an analgesic; the interepithelial nerve-endings are in both cases supplied inadequately with blood, which blood in turn becomes venous unduly early. The effects of interference with the capillary circulation also assert themselves in the central nervous system, and in the nerves, hence the beneficial effect of antipyrin in the neuralgic pains of locomotor ataxia. Again, while, as emphasized by Halliday,[91] one large dose may exalt the spinal reflexes, this may be avoided by administering the drug in increasing doses. The functional exaltation, therefore, is but an ephemeral phenomenon, as I have previously stated.

Pain is now ascribed by physiologists to a common factor. "The cause of pain is always an irritation of the sensory nerves exceeding the normal," says Landois,[92] in his recently published text-book. "All kinds of irritation: mechanical, thermal, chemical, electrical and somatic (inflammatory processes, disturbances of nutrition and the like) may excite pain." It is by indirectly reducing the volume and vitalizing activity of the blood of the irritated area, therefore, that antipyrin reduces, arrests or prevents pain.*

Untoward Effects and Poisoning.—The susceptibility to the effects of antipyrin varies greatly in different individuals. While large doses may be taken without appreciable untoward effects by some, others show evidence of intoxication after taking very small quantities. Again, moderate doses may be taken safely a considerable time, and a small dose suddenly prove toxic. This is due to a corresponding sensibility of the sympathetic center at the time the drug is taken.* This sensibility may be congenital, the so-called "idiosyncrasy," or occur as a result of old age, debility, etc., or it may be acquired by the use of agents which excite this center.* Antipyrin may thus be taken safely a few or many times, even in comparatively large doses, and suddenly even a small dose prove toxic.

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* *Author's conclusion.*

[89] Coppola, Querrolo and Maragliano: Cited by Manquat: *Loc. cit.*

[90] Simon and Hoch: *Loc. cit.*

[91] Halliday: *Loc. cit.*

[92] Landois: "Text-book of Human Physiol.," tenth edition, p. 934, 1905.

The untoward effects of antipyrin are of two kinds: (1) those referred to at the beginning of this section, due to irritation of the vasomotor center, manifested by marked peripheral hyperæmia, and when toxic doses are taken;[*] (2) the characteristic effects of the drug, those due to excessive constriction of all arterioles, including those of the anterior pituitary, heart and skin, the result of violent stimulation of the sympathetic center.[*]

The toxic effects of almost any dose after one or more doses of antipyrin have been taken without discomfort, are so familiar to all practitioners that no evidence need be adduced. The hypersensitiveness of the sympathetic center is not limited to antipyrin. Thus Steinhardt[93] reported a case of intolerance to all drugs of the same class, *i.e.*, quinine, acetanilid, phenacetin and sodium salicylate, tried by him to cure a migraine—all active vasoconstrictors.

So marked is the difference between the two general classes of phenomena produced by the drug that they have been divided into two classes by various writers. Demme, for instance, refers to two periods: an initial period, that of "excitation," and a secondary period, that of "paralysis." Wood[94] states that "it is probable that in toxic doses the drug acts as a primary stimulant and a secondary depressant of the spinal cord." The special senses were also found to be "first stimulated, then paralyzed," by Simon and Hoch.[95]

The symptoms provoked by excitation of the vasomotor center are those of intense capillary hyperæmia,[*] viz., sneezing; burning and swelling of the mouth and throat; nausea and vomiting; abdominal pain and diarrhœa. Skin-eruptions of various kinds, incident upon the imperfect elimination and retention in the cutaneous structures of various toxic wastes; red patches or diffused redness suggesting erythema, the onset of measles or scarlatina, etc.; urticaria, purpura, eczema, bullæ, etc., and even gangrene, may also appear. Chronic poisoning may include any of these phenomena and excitability, tremors and gastric disorders, mental confusion, vertigo and tinnitus aurium.

The morbid phenomena due to excessive excitation of the sympathetic center and the resulting constriction of the arterioles of the pituitary and heart,[*] are those of collapse. The cardiac action becomes more or less depressed and weak; it

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[*] *Author's conclusion.*
[93] Steinhardt: Therap. Monatsch., Bd. x, S. 629, 1896.
[94] Wood: *Loc. cit.*, thirteenth edition, p. 603, 1906.
[95] Simon and Hoch: *Loc. cit.*

may cease suddenly, the heart being arrested in diastole—evidence of its inability to contract upon the blood-stream. The formation of adrenoxidase being reduced owing to deficiency of adrenal secretion,* the respiration becomes hurried, the patient gasping for breath and showing every evidence of marked dyspnœa, the cyanosis becoming deeper as the lethal trend proceeds. Death sometimes occurs from respiratory failure, *i.e.*, before cardiac arrest.

In other cases, the course of events is less acute—the type due to gradual inhibition of pituitary and cardiac function through hyperconstriction of their arterioles.* There is great muscular weakness and finally complete paralysis. The face may lose its dusky hue and become blanched owing to relaxation of the great central trunks and depletion of the superficial vessels, the blood-pressure steadily decreasing. The pulse becomes feeble, fluttering, intermittent and very rapid. The temperature is also lowered, sometimes 5° C. (9° F.). The pupils dilate widely, and vision may become lost along with the other senses. The urine becomes albuminous and has the chocolate-hue of methæmoglobinuria; in the advanced stage, however, there is usually anuria. Somnolence may deepen into unconsciousness and coma, but death is sometimes preceded by convulsions, due to the accumulation of toxic wastes in the spinal system.*

Most of the cases of poisoning reported have occurred during the use of the drug as an antipyretic. "We must not forget," says Manquat, "that it is in typhoid fever that antipyrin, even in small doses, has caused the greatest number of accidents." Moreover, a marked intolerance to antipyrin has been observed after typhoid fever which did not previously exist. In a series of 116 instances of poisoning collected from literature by Hare,[56] acute symptoms are stated to have begun "at once" or "immediately" after the ingestion of the drug 32 times. In 15 of these the symptoms were those of "serious collapse," the phenomena recorded including subnormal temperature, a feeble pulse, etc. The rest, however, all show some evidence of the morbid process primarily provoked by the drug: the typical eruptions, sneezing, heat of the surface, cyanosis, etc., referred to above. The underlying vasoconstriction and the retention of toxic waste products in the dilated capillaries (which products should freely circulate in order to be converted normally into eliminable products), added to this vasodilation, completes the list of factors required to account for the eruptions as well as the other morbid effects. Wechselmann,[57] in fact, was led by a careful study of the question, to ascribe antipyrin eruptions to lesions of the central nervous system, and especially the vasomotor apparatus. Malherbe[58] witnessed a case in which the penis became completely black after taking a dose of 23 grains (1.5 gms.), the same dose he had taken fifteen years for migraine. He refers to a similar case reported by Fournier. Gangrene was observed by Verneuil.[99] The inhibitory influence antipyrin has on life processes, by arresting the circulation in the anterior pituitary and the heart, is shown by the morbid influence on oxygenation previously referred to. Jean and Frédéricq[100] found, moreover, that it reduced the intake of oxygen.

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* *Author's conclusion.*

[56] Hare: "Fever: Its Path. and Treat. by Antipyrin," 1891.

[57] Wechselmann: Arch. f. Derm. u. Syph., Bd. 1, S. 23, 1889.

[58] Malherbe: Jour. mal. cutanées et syphil., July, 1894.

The *treatment of antipyrin poisoning* is described in a special section at the end of this volume.

Therapeutics.—The foregoing facts account for the opposition of experienced clinicians to the use of antipyrin in *fever.* By preventing the access of blood to the capillaries it antagonizes, moreover, the functions of the body's auto-protective mechanism and tends to paralyze the heart.* Much safer drugs are available to counteract *hyperpyrexia* when this threatens to produce hæmolysis, which is very seldom the case.*

It is as an analgesic that antipyrin proves valuable. In *migraine, sciatica, neuralgia,* etc., which, as will be seen, are due to hyperæmia of the nerves *per se,* it produces marked relief by reducing the caliber of their nutrient arteries.* It is useful in *pertussis* by causing constriction of the laryngeal arterioles, thus reducing the local hyperæsthesia.* Its value in *chorea* is accounted for by a corresponding action on the overactive muscles,* a process which explains also the value of antipyrin in *rheumatism,* articular and muscular, and *gout.** It is efficacious also when a localized congestion produces pain; thus in dysmenorrhœa it is sometimes very effective by decreasing the volume of blood circulating in the uterine tissues.* In *epilepsy* and *tetanus* the constriction of the arterioles, by preventing the cerebral hyperæmia and the oxygenizing power of the blood circulating in the cerebro-spinal axis, tends to prevent paroxysms* —an observed fact. Finally, antipyrin can arrest lactation—a normal result of the reduction of blood in the glandular elements which the abnormal constriction of their arterioles entails.*

Large doses of antipyrin, by producing capillary hyperæmia, tend to counteract the beneficial effects of the drug,* and should therefore be avoided.

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* *Author's conclusion.*

[99] Verneuil: Cited by Shoemaker: *Loc. cit.*, sixth edition, p. 717, 1906.

[100] Jean and Frédéricq: Manquat: *Loc. cit.*

ACETANILID.

Physiological Action.—*Acetanilid differs from antipyrin in* that a therapeutic dose excites the sympathetic *center with more* suddenness, and also, but less actively, the *vasomotor center.** *As in the case of antipyrin, however, the general constriction of the arterioles provoked retards the passage of the blood through the capillaries, thus exposing it unusually long to the* reducing action of the surrounding tissues.* The normal relations between oxygen and carbon dioxide in the peripheral capillaries (as in those of the body at large) being modified in that they contain less oxygen and more carbon dioxide than usual, the temperature of their own blood and that of the surrounding tissues is correspondingly lowered.* The effect of acetanilid is ephemeral as compared to antipyrin, however, the cyanosis it produces disappearing promptly after discontinuing its use.

The purely nervous source of the phenomena produced by acetanilid and its constrictor action are shown by the fact that cessation of its use in large quantities will be followed by general hyperæmia and maniacal excitement, due evidently to relaxation of the vessels. A marked case of this kind was reported by Herrick.[101] The resumption of the drug arrested these morbid phenomena. Another interesting example was reported by Stengel and White,[102] in a young woman who took surreptitiously large quantities of the drug four or five years. Although the patient was exceedingly cyanosed, the lips and nails being almost black, the authors state that "the cyanosis disappeared when the medicine was discontinued." Its ephemeral action is plain. Stengel and White also state that "it is not easy to explain the rapid recovery of normal conditions when the drug is withdrawn." Its action on the sympathetic center readily accounts for the result. As soon as the vessels relax, the oxygenation of the blood in the capillaries becomes normal. Lépine[103] had already observed that the cyanosis of acetanilid ceased when the use of the drug was discontinued.

Acetanilid, like antipyrin, by causing engorgement of the capillaries* gives rise to accumulation of carbon dioxide in the latter, and cyanosis, but this is sometimes followed when the use of the drug is prolonged, by the dissociation of hæmoglobin and the formation of methæmoglobin. Not only does the imprisoned blood acquire a muddy brownish color, but the urine may also appear dark brown.

That imprisoned blood is unusually depleted of its oxygen by the tissues is shown by the fact that Lépine and Aubert[104] found that the oxygen was distinctly decreased. The rôle of carbon dioxide as the cause of cyanosis was also shown by Freund,[105] who found spectroscopically no methæmoglobin in a case of *excessive* cyanosis caused by the drug. This represents but a preliminary condition of the blood, however, for methæmoglobin may occur as a result of a still greater loss of oxygen by the blood, *i.e.*, that which *in* the corpuscles *per se* serves to hold the hæmoglobin molecule in combination. While Lépine, Weill[106] and Herczel found that acetanilid transformed hæmoglobin into methæmoglobin, the serum, according to Lépine, does not show the characteristic color of the latter, hence he concludes it must be produced in the red corpuscles. The disintegration of the blood is further emphasized by the fact that, as shown by Hénocque, methæmoglobinic blood can no longer absorb oxygen. Denning[107] recently found that in the dog the formation of methæmoglobin, when 10 grains (0.64 gms.) per kilo of the drug was given, began in thirty minutes and reached its maximum in from four to six hours, the animal dying when 66 per cent. of methæmoglobin was present in the blood. Besides the many cases of methæmoglobinuria reported, cases in which the hæmatoporphyrin was found in the urine (giving it a port-wine color) have also been recorded, that of P. King Brown[108] for instance. This pigment points to a still greater dissociation of hæmoglobin, owing to the abstraction of oxygen.*

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* *Author's conclusion.*

[101] Herrick: Boston Med. and Surg. Jour., Feb. 22, 1906.

[102] Stengel and White: Univ. of Penna. Med. Bull., Feb., 1908.

[103] Lépine: Rev. de méd., vol. vii, pp. 306, 520, 1887.

[104] Lépine and Aubert: Lyon méd., vol. liii, p. 316, 1886.

As is the case with antipyrin, the analgesic property of acetanilid is due to the early conversion of arterial blood into venous blood in the capillaries, including those of the cerebrospinal axis.* The activity of the general cellular metabolism being thus lowered, both the peripheral and central sensory elements are rendered less sensitive.*

Herczel[109] found that in dogs (which can stand large doses) acetanilid caused loss of reflexes in from five to ten minutes. Bokai[110] also found experimentally that the drug paralyzed the sensory elements of the cord. Weill,[111] moreover, noted general anæsthesia in animals under the influence of toxic doses. The anæsthesia here is, of course, but an advanced stage of the process to which the analgesia is due.

Untoward Effects and Poisoning.—As soon as the therapeutic dose is replaced by the moderate or large dose, acetanilid acquires the same properties as antipyrin. It irritates the vasomotor center, and thereby causes the deep arteries to drive blood towards the capillaries.* Among the symptoms are: a full pulse-wave, headache, subdermal swelling and œdema, pruritus, flushing, a scarlatinalike blushing, erythema and other cutaneous disorders, polyuria, and also nausea, retching, vomiting and gastric pain. The increase of arterial blood thus projected into the tissues* produces an increase of metabolic activity therein.

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* *Author's conclusion.*

[105] Freund: Deut. med. Woch., Bd. xiv, S. 834, 1888.

[106] Weill: Thèse de Paris, 1887.

[107] Denning: Deut. Archiv f. klin. Med., Bd. lxv, S. 524, 1899.

[108] P. King Brown: Amer. Jour. Med. Sci., Dec., 1901.

[109] Herczel: Wiener med. Woch., Bd. xxxvii, S. 1021, 1053, 1085, 1887.

[110] Bokai: Deut. med. Woch., Bd. xiii, S. 905, 1887.

[111] Weill: Bull. gén. de thérap., méd. et chir., vol. cxii, p. 150, 1887; thèse de Paris, 1887.

Lépine[112] found that 0.40 gms. (6 grains) per kilo of animal brought on in one-half hour a marked increase of cardiac power, with a rise of blood-pressure. H. C. Taylor experimentally ascertained that 6 grains (0.36 gm.), even when rapidly increased to 40 grains (2.6 gms.) in human subjects, caused a slight increase of urea excretion. Lépine[113] also found experimentally that an increase of urea was produced by the drug, but not invariably. Most suggestive, however, is the investigation of Kumagawa,[114] who found, after exhaustive experiments, that 2 to 3 gms. (30 to 45 grains) did not only increase the nitrogen elimination in the dog, but that 4 to 5 gms. (60 to 75 grains) increased it materially. The increased tissue-waste which these results indicate is readily accounted for by the hyperæmia of all organs which engorgement of their capillaries entails.

The stage of collapse is similar to that caused by antipyrin. It comes on when the sympathetic constriction of the arterioles is sufficiently great to block the circulation of the anterior pituitary and heart.* The symptoms are similar to those that follow extirpation of the adrenals, but aggravated by the fact that the circulation of the entire body is impeded by the reduced caliber of the vessels.* The skin is dusky, cyanotic, or livid; there is profuse sweating; intense weakness or general paralysis; the pulse is very feeble and small and may become thready; the surface temperature may be lowered several degrees, and steadily declines in lethal cases; the respiration is shallow and irregular, artificial breathing affording no relief. Albuminuria, with hæmoglobinuria, methæmoglobinuria or hæmatoporphyrinuria, are also witnessed, but anuria occurs towards the termination. The pupils are widely dilated, the eyes glazed and staring. When the end is near, convulsions—due to the accumulation of waste-products in the blood*—may occur. The heart's action is first weak, then irregular; and death usually occurs from heart-failure, the organ remaining dilated, owing mainly to inadequate renewal of its myocardial blood.*

The mechanism of the cardiac failure here does not differ much from that produced by constriction of the cardiac arterioles produced by other drugs. Instead of being restricted to the heart's vessels, the vasoconstriction is general and the heart is deprived of its blood as effectually. Hence the cardiac arrest in diastole—a process facilitated by the failure of adrenal functions. The cardiac dilation may be observed during life. Stengel,[115] alluding to the case previously referred to, states that "the heart increased tremendously in size," and that the patient "had had several attacks of acute dilatation, with the appearance and subsequent disappearance of a loud systolic murmur, with corresponding increase and subsidence in the intense cyanosis."

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* *Author's conclusion.*

[112] Lépine: Lyon méd., vol. liv, p. 568, 1887.

[113] Lépine: *Ibid.*

[114] Kumagawa: Virchow's Archiv, Bd. cxiii, S. 134, 1888.

[115] Stengel: Boston Med. and Surg. Jour., Feb. 22, 1906.

The *treatment of acetanilid poisoning* is described in a special section at the end of this volume.

Therapeutics.—The indications of acetanilid are precisely the same as those of antipyrin,[116] but it is preferable because small doses do not give rise to the primary stage of excitation and engorgement of the capillaries.*

EXCITATION OF THE VASOMOTOR CENTER AND VENOSITY OF THE BLOOD AS THE BASIS OF SURGICAL ANÆSTHESIA.

Sleep and insensitiveness to pain may also be produced by agents which cause the blood circulating in the central and peripheral nervous systems, the cutaneous capillaries, etc., to become partly venous, metabolic activity being reduced in proportion. This is the characteristic mode of action of anæsthetics.

Chloroform, for example, by stimulating the vasomotor center causes general constriction of all the large vessels of the body, and thereby drives the blood towards the periphery, including the cerebro-spinal system. This produces the familiar stage of excitement followed by that of surgical anæsthesia. The latter is due simply to the fact that the crowding of the blood in the structures mentioned is such that stasis occurs, and, becoming venous *in situ*, fails to sustain local metabolism. The functions of the central nervous system, the peripheral nerve-ends, etc., being in abeyance, sleep and anæsthesia are produced.

The main cause of death during chloroform is its action on the vasomotor center: by stimulating this center excessively it provokes marked constriction of the coronaries of the heart and, by depriving its walls of blood, arrests its action.

The action of *ether* differs from that of chloroform only in that it does not excite the vasomotor center as violently. Though it causes death also by producing excessive constriction of the cardiac coronaries, the constrictor action is more gradual, and the first morbid effect of the heart's deficient contractile power is its inability to project its blood efficiently into the lungs. Oxygenation soon becomes inadequate, and the respiration is the first function to cease in the majority of cases, the rest dying of cardiac arrest.

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* *Author's conclusion.*

[116] *Cf.* this volume, p. 1289.

Nitrous oxide produces anæsthesia by preventing the access of air to the venous blood in the infra-alveolar capillaries, and, therefore, to the adrenal secretion it contains. The latter failing to become oxygenized, *i.e.,* to become converted into adrenoxidase, it passes into the arteries in its normal state and becomes oxygenized at the expense of their blood. Hence the cyanosis immediately produced by nitrous oxide, and the rapidity with which anæsthesia is induced, the entire organism, including the cerebro-spinal system, being supplied with blood deficient in oxygen.

CHLOROFORM.

Physiological Action.—Preceding its true action as an anæsthetic is a short period during which, owing to the irritating action of the chloroform vapor upon the nasal mucous membrane, the heart may be arrested reflexly. The sensory impulses being transmitted from the nasal mucous to the vasomotor center and thence to the cardiac coronaries,* these vessels are constricted sufficiently to deprive the cardiac muscle of the blood it requires to carry on its functions adequately.* Usually there occurs only a temporary depression of the blood-pressure, but occasionally the heart ceases its functions.

The irritating influence of chloroform on the nasal mucosa and the danger of reflex cardiac arrest therefrom is generally recognized, and has been demonstrated experimentally. Thus, Guérin[117] found that if a rabbit be made to inhale chloroform directly through the trachea after tracheotomy, the heart is in no way affected; if, however, the animal be made to inhale it through the nose, the heart is arrested. The presence of vasomotor fibers in the vagus which supplies the coronaries has been shown by Brown-Séquard and subsequently by Porter,[118] and my own researches[119] have shown that what is now regarded as a physiological function, *i.e.,* "inhibition" of the heart, is a pathological condition due to excessive constriction of the coronaries. Kappeler[120] and Laborde,[121] in fact, found that this early inhibition by chloroform could be prevented in animals by cutting the vagus.

The short duration of this phenomenon and its depressing influence upon the heart-muscle have been observed by many investigators. Thus, as stated by Wood,[122] and "as was first proved by the English Chloroform Committee, after the first half-minute of the inhalation of chloroform there is a progressive lowering of the arterial pressure. This has been confirmed by all observers on the lower animals, and Blauel[123] has shown by tonometrical experiments that the same phenomenon occurs in man." Macwilliam[134] also showed that during this very early stage the contractile power of the auricles and ventricles was reduced, and that these chambers were dilated. Striking in this connection is the fact observed by Levy and also Depree,[136] that sudden death may be caused during light chloroformization by injecting even a small dose of adrenalin, which further contracts the coronary terminals, thus depriving the cardiac muscle of blood.

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* *Author's conclusion.*

[117] Guérin: Revue de chir., vol. xiv, p. 915, 1894.

[118] *Cf.* this volume, p. 1185.

[119] Sajous: N. Y. Med. Jour., May 14, 21, 1904.

[120] Kappeler: "Anæsthetica," p. 55, Stuttgart, 1880.

[121] Laborde: C. r. de l'Acad. de méd., May 27, 1890.

[122] Wood: *Loc. cit.*, twelfth edition, p. 94.

[123] Blauel: Beiträge z. klin. Chir., Bd. xxxi, S. 271, 1901.

This period is soon superseded by the preliminary or *first stage* of anæsthesia. This is due to stimulation of the vasomotor center. All the arteries (excepting the arterioles) being thus caused to contract simultaneously, the blood is driven into the smaller vessels and capillaries, and thus enhances the functional activity of all organs,* including the cerebro-spinal and muscular systems. More or less resistance may then be offered by the patient, especially robust men and alcoholic subjects, accompanied by violent movements, muscular rigidity and even spasm, the face being more or less flushed.

According to Arloing,[137] "the early excito-cardiac action is often accompanied by a slight vasodilator excitation, but this is fugacious and is soon replaced by vasoconstriction." Then, "the vascular pressure is high; and there is simultaneously a diminution of the speed of the blood-current" (Manquat).[138] The occurrence of general vasoconstriction was long ago emphasized by Mayer, Asp, Bernstein[139] and others. More recently, Gaskell and Shore[140] obtained vasoconstriction during narcosis which they ascribed to excitation of the vasomotor center. They reached the same result by injecting chloroform into the blood, by applying locally to the medulla, and by transferring the chloroform-laden blood of one animal to another. The heart's action is slowed as the vascular resistance is increased sometimes as much as one-half, as observed by Macwilliam,[141] Bayliss and Starling[142] and others.

What is usually regarded as the *second stage* of narcosis and "surgical anæsthesia," occurs when the engorgement of the arterioles and capillaries becomes such that the blood can no longer freely circulate.* The torpor of the blood-streams in the arterioles and capillaries finally becomes such that the oxygen supplied to the tissues is inadequate and their functional activity is reduced in proportion.* The various sensory terminals and centers lose their sensibility, *i.e.*, become anæsthetic, and, the cerebro-spinal system being supplied with blood containing an unusual proportion of carbon dioxide, sleep and *insensibility are produced.** The same blood circulating in the *spinal cord, nerves,* and muscles,* *general muscular relaxation* occurs, and the reflexes are abolished. *Although the face is* somewhat congested, owing to the cutaneous *hyperæmia, the temperature is lowered* on account of the *deficiency of oxygen in the cutaneous blood.**

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* *Author's conclusion.*

[135] Macwilliam: Jour. of Physiol., vol. xxv, p. 233, 1900.

[136] Depree: British Medical Jour., Apr. 26, 1913.

[137] Arloing: Thèse de Lyon, 1879.

[138] Manquat: *Loc. cit.*, vol. ii, p. 332, 1903.

[139] Bernstein: Untersuchungen z. Naturlehre des Menschen u. d. Thiere. Moleschott, Bd. x, S. 280, 1870.

[140] Gaskell and Shore: Brit. Med. Jour., Jan. 21, 28, Feb. 4, 1893.

[141] Macwilliam: Jour. of Physiol., vol. ix, p. 367, 1888.

[142] Bayliss and Starling: *Ibid.*, vol. xiii, p. 412, 1892.

Arloing[153] found that the general vasoconstriction which occurred during the period of deep anæsthesia was accompanied by slowing of the circulation. The crowding of the blood into the venous channels is shown by the venous pulse noted by Noel,[154] and most easily observed in the external jugulars. The cyanosis sometimes witnessed in this stage points to inadequate renewal of oxygenated blood in the peripheral capillaries; it represents an advanced stage of this condition. Saint-Martin[155] found that during this stage, *i.e.*, during complete anæsthesia, there was a reduction of oxygen in the blood and an excess of carbonic acid.

Untoward Effects.—This semi-venous condition of the blood tends to inhibit the functions of all organs, but the most dangerous factor in this connection is excessive excitation of the vasomotor center.* As the cardiac coronaries take part in the general vasoconstriction provoked by chloroform, this anæsthetic tends to cause inhibition of the heart proportionally as the vasoconstriction is marked.* The circulation in the pituitary body, the adrenal center, and the adrenals themselves being also reduced in proportion, chloroform tends likewise to hamper the functions of these organs and to diminish the secretory activity of the adrenals, and thus to reduce both the contractile energy of the cardiac walls and the formation of adrenoxidase.* Death may, therefore, be caused in two ways by chloroform: (1) by primary cardiac arrest due to hyperconstriction of the coronaries; (2) by primary arrest of respiration due to paralysis of the adrenal center and the adrenals.* Both the cardiac and the respiratory functions may also fail simultaneously.

The cessation of either the cardiac or respiratory functions is preceded by a rapid, weak, irregular and fluttering pulse, and increasing shallowness and irregularity of the breathing. When the functions cease, either singly or unitedly, the general vasoconstriction is relaxed,* and the blood recedes from the periphery to the now dilating central trunks, causing extreme pallor and a ghastly grayish hue. The temperature falls steadily with the blood-pressure; the pupils, contracted when the carbon dioxide ratio of blood is low, and slightly dilated when it is becoming high, now dilate widely and death follows.

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* *Author's conclusion.*

[153] Arloing: *Loc. cit.*

[154] Noel: Bull. de l'Acad. roy. de Belgique, 3 série, vol. x, p. 785, 1876.

[155] Saint-Martin: "La Respiration," Paris, 1893.

Macwilliam[156] found that out of 357 deaths due to chloroform collected by the Lancet Commission, cardiac failure had occurred 227 times; respiratory failure, 80 times; and failure of both functions at the same time, 77 times. H. C. Wood, in his address before the Berlin International Congress (1890), had previously reached the conclusion that chloroform was capable of causing death either by cardiac or respiratory failure, but especially by cardiac arrest when the heart was feeble. Commonly, however, both functions were abolished at about the same time. The more recent investigations, of which but a few of the more striking can be mentioned here, have fully sustained this opinion. Cardiac inhibition, we have seen, is due to excessive constriction of the cardiac arteries, particularly the coronaries, through vasomotor impulses transmitted by way of the vagus. In 120 experiments in dogs, E. H. Embley[157] found that "respiration was always continued in fatal cases till after all hope of recovery was abandoned." He concluded that the cardiac arrest "was due to stimuli passing down the vagi, for, (*a*) it never occurred in animals in which the vagi had been previously divided; (*b*) when occurring in animals with intact vagi, it immediately disappeared upon section of both of them." Moreover, he "never failed (5 cases) to occasion fatal syncope in a sufficiently chloroformed animal by excitation of one or both vagi by the interrupted current." Schäfer and Scharlieb[158] found the heart arrested in diastole and more or less filled with blood, the "paralytic dilatation" of Lauder Brunton and others, and that it was the "inhibitory mechanism which is brought into play by the action of chloroform."

That respiratory failure is due to adrenal insufficiency also caused by vasoconstrictor interference (a true adrenal inhibition) and the consequent deficiency of adrenoxidase in the blood, is shown by the marked reduction of the blood's oxygen ratio. Both Paul Bert and de Saint-Martin found that during the stage of true anæsthesia the blood steadily becomes poorer in oxygen. The latter investigator observed, moreover, that carbon dioxide was markedly increased in anæsthetized animals. While the normal proportion varies from 1.45 to 1.88 c.c. per litre, during chloroform narcosis it reached 6.9 c.c. per litre. The reduced oxygenation is further shown by the fact that the temperature is reduced. Kappeler[159] found that when inhaled from 15 to 40 minutes, chloroform reduced it from 0.2° to 1.1° C. (0.36° to 2° F.), and that prolonged anæsthesia sometimes caused a fall of 5° C. (9° F.). Both the absorption of oxygen and the elimination of carbon dioxide are dependent, we have seen, upon the quantity of adrenoxidase the blood contains. The fact that the adrenal secretion also contributes to the heart's contractile energy explains, moreover, why a deficiency of this secretion may, in the presence of impending cardiac inhibition, cause both the cardiac and respiratory functions to fail simultaneously.

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* *Author's conclusion.*

[156] Macwilliam: *Loc. cit.*

[157] E. H. Embley: Jour. of Physiol., vol. xxviii, Nos. 1 and 2, p. 1, 1902.

[158] Schäfer and Scharlieb: Proceedings of the Physiol. Soc., 1902.

[159] Kappeler: *Loc. cit.*

Hare[140] aptly defines the recession of blood from the periphery as follows: "The cause of death from chloroform is usually vasomotor depression, whereby the arterioles allow the blood to pass too freely into the great blood-vessel areas, and, as a result, the man is suddenly bled into his own vessels as effectually as into a bowl." Shore and Gaskell[141] ascertained that a large number of curves of the Hyderabad Commission pointed directly to heart-failure as the cause of the fall of pressure. But we must not overlook the fact that, as I have shown above, *this is due to excessive vasoconstriction.*

The *treatment of chloroform poisoning* is described in a special section at the end of this volume.

Danger Signals.—The untoward effects produced by chloroform, in the light of the foregoing analysis, are of two kinds, though tending to destroy life by the same morbid process. The first of these, *reflex* arrest of the heart through the vasomotor center,[*] can be prevented by avoiding irritation of the nasal mucous membrane. This danger may be entirely eliminated (1) by spraying a 10-per-cent. solution of cocaine over the nasal mucosa ten minutes before the use of the anæsthetic is to begin; and (2) by administering very small quantities (the drop method) of the latter, along with a free supply of air. It is to be borne in mind that it is as a *drug* that chloroform acts upon the vasomotor center, and that the suffocation which deprivation of air involves only tends to increase the danger of the procedure.[*]

When a case assumes a lethal trend during the period of full anæsthesia, the cardiac inhibition is brought on, we have seen, by excessive but direct stimulation of the vasomotor center.[*] The death-dealing factor being excessive constriction of the coronaries,[*] this can be prevented by watching the behavior of the arteries elsewhere: (1) the pin-point pupil is the extreme limit of safety, and indicates that the blood in the vessels that supply the iris is inadequately renewed, owing to excessive vasoconstriction;[*] (2) the respiration is one of the first signs of weakening of the heart, since the venous blood is inadequately driven to the alveoli[*] and the automatic regular rhythm is replaced by irregular or short breathing, and sometimes stertor; (3) a full pulse-wave indicates a corresponding condition of the cardiac coronaries;[*] any diminution of expansion of the artery indicates a similar narrowing of these cardiac vessels;[*] (4) the turgescence of the veins of the neck and face indicates the degree of constriction to which the arteries of the system at large are being submitted;[*] *marked vascular turgescence is a threatening sign.*

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[*] *Author's conclusion.*

[140] Hare: Therap. Gaz., Feb. 15, 1897.

[141] Shore and Gaskell: *Loc. cit.*

Clinical experience amply sustains the fact that the pupil, the respiration and the circulation must be watched while administering chloroform.

ETHER.

Physiological Action.—The physiological action of ether differs only from that of chloroform in that it excites less violently the vasomotor center.[*] Its true action is preceded, as in the case of chloroform, by a morbid phenomenon due to the irritating action of the ether fumes upon the nasal mucous membrane, viz., temporary lowering of the blood-pressure due to reflex contraction of the cardiac coronaries[*] and depression of the heart's contractile power through ischæmia of its walls. This reflex coronary constriction, provoked through violent sensory impulses transmitted by the nasal branches of the fifth pair to the vasomotor center,[*] is sufficient in some cases to prove fatal.

Cushny[142] states that "the first change observed in the blood-pressure tracing after chloroform or ether is often a slowing or even a temporary standstill of the heart." H. C. Wood[143] says also that the primary arrest of respiration during the first stage "is undoubtedly due to a local irritation of the mucous membrane of the air-passages." Kratschmer[144] prevented it "by previous section of the trigeminal nerves." We have seen, moreover, that it was by passing a current from the nasal mucous membrane to the bulb that the brothers Weber inhibited the heart. The violent excitation of the sensory trigeminus being transmitted to the vasomotor center, and thence to the coronaries by the vasomotor fibers in the vagus (Brown-Séquard, Porter), the heart, no longer adequately fed by its arteries, is unable to contract with its usual power upon the blood-column, and may even remain dilated. The rôle of the vasomotor fibers of the cervical vagus is well shown by the fact that Hare[145] found that preliminary division of the vagus prevented the respiratory arrest due to ether irritation of the respiratory passages.

The influence of reflex action in the morbid process is emphasized by the fact that Laborde found that the application of a weak solution of cocaine to the nasal cavities prevented the untoward symptoms. This was confirmed by Rosenberg[147] and others. The arrest of respiration, during the preliminary stage, is the normal outcome of the weakened or arrested cardiac action: the heart is no longer able to propel the blood to the lungs.

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[*] *Author's conclusion.*
[142] Cushny: *Loc. cit.*, fourth edition, p. 158, 1906.
[143] Wood: *Loc. cit.*, thirteenth edition, p. 88, 1906.
[144] Kratschmer: Sitz. d. k. Acad. Wien., Abt. II, 1870.
[145] Hare: Univ. Med. Mag., Apr., 1889.

The first effect of ether as an anæsthetic is to stimulate directly the vasomotor center.* The general vasoconstriction which ensues forces the blood into the smaller arteries, and thence into the cerebro-spinal and peripheral capillaries.* This causes flushing and warmth of the surface, a sense of exhilaration, of physical lightness, visions, hallucinations of various kinds, roaring, hissing and ringing in the ears. Towards the end of this stage movements of the arms and legs may occur, the patient striving perhaps to rise. Shouting, raving, laughter and other manifestations of physical and mental excitement may also occur at this time. The muscles are then rigid.

According to Wood, Sr., "the first effect of ether is usually to cause a pronounced rise in the arterial pressure, which is commonly maintained even through a prolonged ether narcosis." The vasoconstriction must be very marked, since, as stated by Cushny[148] and other observers, the face "may be suffused and cyanotic." Eulenburg[149] found the knee-jerk increased evidence that the spinal centers are unduly supplied with blood. The cutaneous hyperæmia and cyanosis (successive steps) are normal results of the constriction, here as elsewhere, of the muscle-coated vessels, while the capillaries, deprived of muscles, become engorged, congested and dilated. Hence the initial period of excitement. Marchetti[149a] attributes the high blood-pressure to a direct action of the ether on the adrenals.

The stage of true anæsthesia comes on when the circulation in the capillaries of all organs is sufficiently slowed by the general vasoconstriction to supply them inadequately with oxygen.* Their functional activity is reduced in proportion. The tactile end-organs of the skin and the sensory paths of the spinal cord are the first to lose their sensibility, and anæsthesia may thus begin before the end of the stage of excitement. The cerebral functions are then suspended, narcosis supervening; soon thereafter all voluntary motor functions are also inhibited, as manifested by general relaxation of the skeletal muscles. Although the face is congested, the general temperature is somewhat lowered, owing to the inadequate oxygenation of the peripheral structures.* The involuntary or automatic motor functions are the last to yield, the respiration being slow, deep and rhythmic, the pulse somewhat quickened though stronger —in cases proceeding safely.

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* *Author's conclusion.*

[147] Rosenberg: Cited by Willy Meyer: Annals of Surgery, Jan., 1896.

[148] Cushny: *Loc. cit.*, fourth edition, p. 154, 1906.

[149] Eulenburg: Centralblatt für med. Wissen., Bd. xix, S. 97, 1881.

[149a] Marchetti: Riforma Medica, June 12, 1915.

Vasoconstriction persists, we have seen, "even through a prolonged ether narcosis," according to Wood, and "may continue until manifest failure of respiration." Hence, narcosis must occur simultaneously with vasoconstriction. The reddish, *i.e.*, hyperæmic hue of the face, neck, etc., betokens the presence of engorgement of the peripheral capillaries, while the cyanosis occasionally observed shows that the blood contained in these vessels is deficient in oxygen. Intense venous congestion was found post-mortem by Hammond Smith.[180]

Untoward Effects.—When, from reddish and suffused, the face becomes pale or livid, either the heart or the respiration has failed. Death may thus be caused in two ways: (1) by cardiac arrest, due to excessive stimulation of the vasomotor center and constriction of the cardiac coronaries beyond limits of safety to the heart-muscle.* The heart-walls being inadequately supplied with blood,* they are no longer able to contract upon their contents. This morbid process is aggravated by the increased resistance of the blood-column which the general vascular tension entails,* and by the venous condition of the blood.* (2) By arrest from the same causes, excessive vasoconstriction and venosity of the blood, of the functions of the pituitary body.* The functions of the adrenals being inhibited through paresis of their center, the proportion of adrenoxidase (oxyhæmoglobin) formed becomes inadequate to sustain life,* and the patient dies of respiratory failure. This is the most frequent cause of death in ether anæsthesia.

The chances of death are increased when, instead of admitting air with the anæsthetic, the latter is administered pure. The adrenal secretion then passes the pulmonary alveoli in its pure state, and the general vasoconstriction is augmented artificially as it is by nitrous oxide.*[181] Cyanosis suggests the presence of this condition (since the adrenal secretion on entering the arteries in its normal states at once robs their blood of oxygen), and the supply of air should be increased when this symptom appears.*

Both cardiac and respiratory failure are at once followed by general vasodilation. The blood receding into the great central trunks suddenly depletes the peripheral capillaries.[1] Hence the pallor and lividity, the wide dilation of the pupils and other phenomena denoting approaching dissolution.

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* *Author's conclusion.*

[180] Hammond Smith: Brit. Med. Jour., Jan. 8, 1898.

[181] *Cf.* this volume, p. 1304.

The phenomena of cardiac inhibition are distinctly demonstrable experimentally. Cushny states[152] that the frog's heart, under ether, "beats more slowly and more weakly, and at the same time undergoes a certain amount of dilatation." These are the typical signs of inhibition. "Eventually," writes the same author, "if the administration be carried far enough, the blood-pressure falls to zero and the heart ceases to beat. The way in which this fall of blood-pressure is produced has been the subject of prolonged discussion, but it is now generally recognized that the weakness of the heart is the chief factor." . . . . . "The effects on the mammalian heart are very similar." Obviously, being ischæmic, the heart ceases to sustain the *vis a tergo* motion of the blood, and the functions of the general vasomotor center cease. The intensity of the vascular constriction is emphasized by the observation of Sansom[153] that "the vessels of the frog's web are thrown into persistent spasm by the inhalation of ether," while the transition is well exemplified by the researches of Bowditch and Minot[154] in mammals, that "the vasomotor centers are at first stimulated and afterward depressed."[155] Vasoconstriction of the cardiac arteries, *plus* active resistance of the blood-column, *plus* deficient adrenal secretion, and *plus* the venous condition of the blood, amply account for the cardiac failure.

Yet, experienced anæsthetists generally agree in ascribing the majority of deaths to failure of the respiration, *i.e.*, to asphyxia. The venous condition of the blood is strictly in accord with the interpretation of the morbid process I submit above. J. Chalmers Da Costa and Kalteyer,[156] in a comprehensive study of the blood-changes induced by ether, write as follows: "The hæmoglobin is always reduced absolutely; in some instances there is an apparent increase, but this rise in the percentage of hæmoglobin is never parallel with the rise in the number of red blood-cells. The individual corpuscular value is therefore reduced." The influence of the deficiency of adrenoxidase is also well shown by the observation of Sweet[157] that a comparison of the curve of the blood-pressure of a dog under ether with that of a dog from which the adrenals have been removed is the same, though the gradual fall occurs somewhat sooner in the adrenalectomized animal.

The *treatment of ether poisoning* is described in a special section at the end of this volume.

Danger Signals.—This interpretation of the manner in which ether produces untoward effects suggests precautions which, if strictly observed, would tend materially to prevent them and decrease the number of fatalities.* Ether being a violent irritant, the danger of causing reflex arrest of the heart can be prevented (1) by avoiding the sudden onslaught of its dense vapor upon the upper respiratory tract which the use of the folded towel or the cone insures; (2) by spraying a 10-per-cent. solution of cocaine into the nasal cavities about ten minutes before the administration of the anæsthetic is begun; and (3) by administering a very small quantity at first along with a free supply of air. As it is through its direct action upon the vasomotor center that ether produces anæsthesia, a small quantity, as given in the "drop method," suffices to start with. Gradually, as the patient yields to the influence of the anæsthetic, the quantity is increased, air being always admitted freely. Struggling is prevented by this plan, since this is usually prompted by a feeling of suffocation.

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* *Author's conclusion.*

[152] Cushny: *Loc. cit.*, fourth edition, p. 160, 1906.

[153] Sansom: "Chloroform, Its Action and Administration," Phila., 1866.

[154] Bowditch and Minot: Boston Med. and Surg. Jour., May 21, 1874.

[155] Cited by Wood: *Loc. cit.*, eleventh edition, p. 94, 1900.

[156] Da Costa and Kalteyer: Annals of Surgery, Sept., 1901.

[157] Sweet: Annals of Surgery, Oct., 1910.

The dangers of the period of deep anæsthesia are commensurate with the proportion of CO_2 in the blood, and the degree of tension to which the arteries are submitted.* When, therefore, the patient is anæsthetized, the color of the skin, the "flush"—which indicates that the blood circulating in the arteries is sufficiently arterial to sustain vital functions of all organs, including the pituitary body and the heart—should be closely watched, and any indication of duskiness (not awaiting cyanosis) serve as an indication of a greater air supply.* To await dilation of the pupil, weakening of the pulse, respiratory distress, etc., is a dangerous feature of the prevailing technique, since these are the signs of cardiac and pituitary inhibition.*

NITROUS OXIDE.

Physiological Action.—Nitrous oxide produces anæsthesia by preventing the access of oxygen to the pulmonary blood, *i.e.*, to the venous blood containing the adrenal secretion.*

Dastre[198] states that "pure nitrous oxide anæsthetizes, but it kills by causing asphyxia; mixed with air it does not kill, but it does not anæsthetize." The view that its effects are due to asphyxia was opposed by Goltstein[199] on the plea that nitrous oxide provoked sensory and reflex phenomena which were absent when an inert gas was used. H. C. Wood and Cerna[200] in a series of experiments found, however, that the circulatory phenomena of nitrous oxide anæsthesia were very similar to those caused by inhalations of pure nitrogen or by mechanical asphyxia, and that the addition of so small a portion of oxygen as 3 per cent. almost doubled the time for the production of anæsthesia, while 5 per cent. lengthened it nearly eight times. A subsequent study by Wood[161] confirmed the conclusion that nitrous oxide produced anæsthesia by cutting off the supply of oxygen. His results fully confirmed those formulated by Ludimar Herrmann in 1864[162] and other investigators since, that nitrous oxide acted simply as an asphyxiant. Indeed, Colton,[163] E. Thomson[164] and Wood have all found experimentally that animals lived no longer in nitrous oxide than in hydrogen, nitrogen or a vacuum.

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* *Author's conclusion.*

[198] Dastre: "Les Anesthésiques," Paris, 1890.

[199] Goltstein: Arch. f. d. ges. Physiol., Bd. xvii, S. 311, 1878.

[200] H. C. Wood and Cerna: Therap. Gaz., Aug., 1890.

By preventing the access of oxygen-laden air to the lungs, nitrous oxide prevents the conversion of the adrenal secretion into adrenoxidase. The secretion, by penetrating the arteries in its original condition, appropriates the oxygen of their blood, supplements the tissues in converting it into venous blood.* Hence the promptness with which cyanosis is produced.*

Hermann, Jolyet and Blanche,[165] Goltstein, MacMunn,[166] Buxton,[167] Halliburton and Kemp,[168] all assert that nitrous oxide does not combine with hæmoglobin.[169] The cyanosis, therefore, must be due to the familiar cause, *i.e.*, the accumulation of carbon dioxide. Yet, Oliver and Garrett[170] found in the course of experiments upon dogs that during nitrous oxide anæsthesia there was "a marked deficiency of oxygen and no excess of carbonic acid" in the blood. Obviously, the loss of oxygen was not due to tissue metabolism; some substance other than the tissues must have absorbed the oxygen. That this substance must be the adrenal secretion is evident; not only is it endowed with marked affinity for oxygen, but the oxygen-laden air being replaced by nitrous oxide, the secretion necessarily passes the pulmonary air-cells without taking up oxygen. *Venous* blood, laden with adrenal secretion, soon circulates in the arteries. Hence the venous character of the arterial blood.

The temporary exhilarating effect of nitrous oxide, as manifested by hilarity, physical lightness, the sensation of well-being, etc., and the aural rumbling or buzzing are due to the ephemeral congestion of the cerebral and upper spinal centers which precedes complete anæsthesia. This congestion is produced mechanically: the adrenal secretion on entering the arteries provokes a fictitious vasoconstriction which progresses with the blood containing it from the larger arteries to the smaller.* The terminal arterioles and the capillaries which receive their blood thus become engorged, and the nervous elements they supply are inordinately excited as long as the blood remains arterial.*

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* *Author's conclusion.*

[161] Wood: Dental Cosmos, May, 1893.

[162] Ludimar Herrmann: Arch. f. Anat. u. Physiol., 1864.

[163] Colton: "The Physiol. Action of Nitrous Oxide Gas," Phila., 1871.

[164] E. Thomson: Phila. Med. Times, Nov. 15, 1873.

[165] Jolyet and Blanche: Arch. de physiol., T. v, p. 364, 1873.

[166] MacMunn: Dublin Jour. Med. Sci., Sept., 1879.

[167] Buxton: Trans. Odontol. Soc. of Great Britain, vol. xix, 1887.

[168] Kemp: Johns Hopkins Univ. Circ., June, 1897.

[169] Cited by Wood: *Loc. cit.*, thirteenth edition, p. 85, 1906.

[170] Oliver and Garrett: Lancet, Sept. 9, 1893.

Oliver and Schäfer[171] have shown that the adrenal extract powerfully contracts the blood-vessels. Penetration of the adrenal secretion into the arteries, as stated above, must therefore not only raise the arterial pressure, but the process being an abnormal one, it cannot but present unusual characters. Referring to his own elaborate experiments, H. C. Wood[172] says that he found "that the inhalation of nitrous oxide is usually followed by a rise of arterial pressure, accompanied by a great disturbance of the pulse." The "rise and fall of the arterial pressure" was found to "vary remarkably, not only in different inhalations, but at different periods of the same inhalation. Sometimes the rise was sudden, sometimes it was gradual; sometimes it was maintained until near death; sometimes it was interrupted very early; sometimes it was not very well marked; sometimes it was enormous." The engorgement of the cerebral capillaries is well known by the fact that Amory[173] found in cerebrometric experiments in dogs, that "there is during anæsthesia, increased blood-pressure in the cerebrum with stasis in the capillaries." This morbid rise of blood-pressure and the resulting cerebral hyperæmia may cause fatal cerebral hæmorrhage in a predisposed subject, as shown by a case reported by Hare.[174]

Anæsthesia of the peripheral structures occurs before narcosis is complete because the cutaneous capillaries are invaded sooner by venous blood than the cerebro-spinal cells.* When narcosis is complete, the venous blood has penetrated the cerebral neurons, and by lowering their metabolism correspondingly inhibits their functional activity. An artificial sleep is thus produced.*

The pyramidal cells of the cortex, we have seen,[175] alter their form during sleep. Goddard[176] found that in puppies decapitated after a night's rest, the heads dropping at once in fixing solutions, "it was difficult to find a single varicosity on the dendrites," while in very sleepy and tired puppies, a cell whose processes were not more or less varicose could hardly be found. Demoor[177] noted similar effects in specimens of gray substance from a morphinized dog; the processes or gemmules had disappeared, while a specimen taken before the morphine had been given was covered with regularly distributed gemmules. We have, evidently, in these processes, manifestations of erethism. As, in the light of my views, the dendrites, axis-cylinders, fibrils, etc., are but nervous capillaries, the penetration in them of venous blood cannot but subdue this erethism. Goltstein observed that the spinal reflexes of frogs were reduced, and attributed this to a direct action of the nitrous oxide; but the penetration of venous blood in the cellular elements finely accounts for this phenomenon without granting this gas direct anæsthetic properties. Their functions are merely in abeyance, as are those of all the cells of the cerebro-spinal axis. "During sleep," says Landois,[178] "there is diminished irritability of the entire nervous system." . . . . . . "During sleep stronger irritation is required in order to excite reflexes."

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* *Author's conclusion.*

[171] Oliver and Schäfer: *Loc. cit.*

[172] H. C. Wood: *Loc. cit.*, thirteenth edition, p. 84, 1906.

[173] Amory: N. Y. Med. Jour., Aug., 1870.

[174] Hare: Therap. Gaz., Dec. 15, 1896.

[175] *Cf.* vol. 1, p. 521.

[176] Goddard: Jour. of Compar. Neurol., Nov., 1898.

[177] Demoor: *Cf.* vol. 1, p. 520.

Untoward Effects.—Death may be caused in two ways, (1) by cardiac arrest, owing to the resistance imposed upon the cavities of the heart by the excessively constricted arteries,* (2) by respiratory failure owing to the nonconversion of the adrenal secretion into oxidizing substance.*

Oliver and Garrett[179] found in dogs killed with nitrous oxide, that the arteries were empty and the veins engorged. This is readily accounted for by the marked vasoconstrictor action of adrenal secretion which, as stated, penetrates the arteries without being converted into the adrenoxidase.* The blood was necessarily forced into the veins. The same experimenters found all the heart cavities distended—a normal result of the intense back-pressure imposed upon this organ. As to the second cause of death, *i.e.*, the non-formation of the adrenoxidase, Wood states,[180] referring probably to his experiments, that "death always occurred from respiratory paralysis, the heart continuing to beat powerfully after respiration had ceased and the arterial pressure had fallen very low." The heart is not deprived of adrenal secretion, hence its powerful resistance; the respiratory process loses its aid, however, hence its failure. Oliver and Garrett found the lungs collapsed.

The *treatment of nitrous oxide poisoning* is described in a special section at the end of this volume.

Danger Signals.—The mortality of nitrous oxide is practically *nil* (about 1 in 150,000), owing mainly to the fact that it is used only for minor operations, the extraction of teeth, etc. As it unquestionably produces asphyxia, its prolonged use is contraindicated. This drawback is partly overcome, however, by Cryer's apparatus, which enables the patient to inhale a certain proportion of oxygen along with the nitrous oxide gas, and also to administer at once nothing but oxygen when danger signals appear.

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* *Author's conclusion.*

[178] Landois: *Loc. cit.*, tenth edition, p. 778, 1905.

[179] Oliver and Garrett: *Loc. cit.*

[180] Wood: *Loc. cit.*, thirteenth edition, p. 86, 1906.

CHAPTER XXI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*).

REMEDIES WHICH DEPRESS THE FUNCTIONS OF THE ADRENAL, VASOMOTOR AND SYMPATHETIC CENTERS.

All the drugs analyzed so far which were shown to produce their effects by influencing nerve-centers, were found to do so by stimulating those centers. Evidence will now be submitted to the effect that by means of other remedies we can produce a contrary action, *i.e.*, depress these identical functions —profitably where excessive erethism prevails—each agent described being likewise capable of doing so in a characteristic manner.

Even the test-organ and the adrenal center can thus be controlled through our drugs. Indeed, Nature seems to have provided a substance, *arsenic*, which, merged in with the thyroidase probably, tends to reduce markedly its sensitiveness. Whether we are dealing with a physiological constituent of the body or not, the fact remains, that it is found normally in greatest quantity in the thyroid gland and that it antagonizes directly the action of thyroid extract. Whereas the latter promotes catabolism and emaciation, arsenic prevents wear and tear of the tissue-cell. Thyroid breaks down fats; arsenic conserves them. The many beneficial effects it produces in cutaneous, nervous, and blood diseases are, we will see, accounted for by this one central action.

Another, though of course artificial, agent of this class is *chloral*, which causes sleep by rapidly depressing the test-organ, and through it therefore, general metabolism. The muscularis of all vessels being the seat of less active exchange, it becomes relaxed, and the brain being deprived of some of its blood owing to accumulation of the latter in the great channels of the splanchnic area, sleep is promoted not only because of the diminution of blood in it, but because the blood itself is deficient in adrenoxidase. Here, again, marked general phenomena are due not to action on peripheral structures, but upon a general center.

Another form of depression, the converse, as it were, of the erethism procured by adrenalin and antitoxin, is that caused by *alcohol* in all but small doses. The stimulating property with which it is credited is an ephemeral phenomenon, as we will see, due to the sudden excess of heat energy developed while it is being oxidized by the oxygen-laden adrenoxidase. The process itself brands alcohol as a depressant, however, since it is at the expense of the tissues that it robs the blood of this gas. It is because of the misinterpretation of the rôle of energy in the organism and of the prevailing misconception of the nature of the vital process, that it is regarded as a food. As a remedy it has but little claim to recognition: beyond the spurt of proteolytic activity acquired by the blood's trypsin which a small dose of ethyl alcohol procures by liberating heat-energy, its trend is to paralyze the body's protective functions, as shown in various ways.

The test-organ is not, however, the only center whose functions may be depressed directly or indirectly by drugs. As stated by Professor Charles Richet,[1] "all toxics (with rare exceptions, CO_2, for instance, and a few other hæmoglobin toxics) are hardly poisonous otherwise than through their action upon the *nerve-cell.* In the organism, the nerve-cell, to the detriment of other cells: muscular, glandular, epithelial, is the most sensitive to toxic action. These laws of excitation, then of depression of the nerve-cell by poisons, are, therefore, very general and applicable to almost all poisons." This does not necessarily mean that nerve-centers are alone influenced in this manner, but it is self-evident that being the most highly organized of nervous structures, they should prove more sensitive to the action of toxics than either subsidiary centers or ordinary nerve-cells.

Richet refers, however, to the secondary depression produced by excitants, having shown in 1881 that even strychnine could be converted into an anæsthetic if the animal's life were prolonged sufficiently long. It is probable that all depressants stimulate primarily, though so slightly in some instances, that the effects of this stimulation are not perceived.

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[1] Chas. Richet: "Dictionnaire de Physiol," T. iv, 1900.

The mode of action of depressants on vascular centers is illustrated by the effects of *bromides* on the vasomotor center, and concomitantly, doubtless, upon the subsidiary spinal centers. Being depressed directly by these salts, the general center allows the vessels of the entire organism to dilate. The blood being thus caused to recede from all peripheral structures, the skin, cerebro-spinal system, etc., to collect in the great central channels, the "depressomotor" influence of these salts becomes self-evident. By this depletion of the peripheral structures, including the pituitary body, the functions of all centers, including the adrenal center, are likewise depressed, and the production of adrenoxidase being correspondingly reduced, general nutrition is impaired. Hence the trophic disorders of bromism. We have here much the same process as that awakened by chloral, but brought about in a different way. The therapeutic kinship of these two drugs is well known.

In *veratrum viride* we have a drug very similar in action to the bromides. By its direct and depressing action on the vasomotor center, it lowers the arterial tension to such a degree, that it "bleeds the patient into his own vessels." The ischæmia of the pituitary body and the skin produced by large doses, so inhibits catabolism, however, that toxic wastes accumulate in the blood, including that circulating in the cerebro-spinal system, an action which causes a rise of the blood-pressure. We thus have the curious example of a drug which in therapeutic doses lowers the blood-pressure and in toxic doses raises it, thus counteracting its own physiological action—with threatened pituitary and cardiac inhibition if prolonged.

Depression of the sympathetic center is illustrated by three well-known agents, prominent among which is *aconite.* The general dilation of the arterioles thus produced allows an excess of arterial blood to enter the capillaries in general. When full doses are given, this marked though passive capillary hyperæmia excites the peripheral end-organs of sensibility and tingling is caused, besides flushing, headache, etc. In poisonous doses, aconite also depresses, then paralyses, the test-organ and *through it the adrenal center. The formation of adrenoxidase being arrested, the patient dies asphyxiated.*

Amyl nitrite likewise depresses the sympathetic center, and by thus causing dilation of the arterioles causes the familiar flushing, increased heart-action, etc. It differs from aconite in that when given in large doses it depresses the vasomotor center, thus causing ischæmia of the peripheral organs and, therefore, the hypothermia and cyanosis sometimes witnessed. The remarkable benefit amyl nitrite affords in angina pectoris finds its explanation in the reduction of vascular tension which dilation of all the arterioles of the body produces, for while the volume of blood admitted into the capillaries of the heart is augmented, the pressure behind the blood-columns as a whole is decreased. *Nitroglycerin* is the counterpart of amyl nitrite as to physiological action, and affords an admirable means for the perpetuation of the beneficial, though fugacious, effects obtained with the latter remedy.

Creosote and kindred agents are shown to combine two seemingly antagonistic actions, viz., to depress the sympathetic and vasomotor centers and excite the adrenal center. In truth, this is but a normal result of the fact that these remedies are treated as foreign and harmful agents by the test-organ, and that it incites a protective reaction which entails the appearance of an excess of adrenoxidase, and, therefore, of auto-antitoxin, in the blood. The beneficial effects of therapeutic doses are readily accounted for by these two properties: by causing a vascular relaxation, creosote not only counteracts excessive vascular tension—a deadly phenomenon in lobar pneumonia, for instance—but the blood which penetrates through the dilated arteries into the diseased areas being unusually bactericidal and antitoxic, the curative process is directly activated.

ARSENIC.

Physiological Action.—Arsenic, which, like other remedies is taken up by leucocytes, is the direct (and probably the physiological) antagonist of thyroidase as far as the stimulating influence of the latter on the test-organ is concerned.* By depressing, through this organ, the functional activity of the adrenal center, it restrains the production of adrenal secretion and, therefore, the formation of adrenoxidase.[*] This reduces general oxygenation correspondingly.[*]

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* *Author's conclusion.*

Besredka[2] found that the trisulphide of arsenic when injected into the peritoneum of rabbits was taken up by leucocytes, in the interior of which these yellowish-red grains could readily be seen to break up into smaller granules, and then to disappear. Gautier[3] found arsenic in various structures, the thyroid, thymus, mammary gland, the skin, hair and nails containing the most, and incorporated with the nucleo-proteids and iodine. It will doubtless prove to be a component of thyroidase.[*]

The constitutional effects of arsenic are evidently of central origin. "There is accord between the experimenters in regard to the cause of the final arsenical paralysis," writes Wood, "all finding that it is produced by a direct action of the poison upon the nerve-centers." As stated by Cushny, paralysis is elicited in frogs by arsenic "much sooner than by arrest of the circulation by excision of the heart." The drug must, therefore, act on the nerve-centers from the start.

That it is the adrenal center which it depresses is shown by the fact that, as stated by Cushny, "arsenic lessens oxidation of the tissue." This is further emphasized by the observation of Bédart and Mabille[4] and Ewald[5] that it antagonizes the effects of thyroid extract, which, as we have seen, powerfully enhances oxidation. According to Hutchison,[6] for instance, the effect of thyroid extract is "to increase oxidation in the body; it makes the tissues, as it were, more inflammable, so that they burn away more rapidly," a conclusion amply sustained by evidence adduced in the first volume. Conversely, as observed by Lauder Brunton,[7] arsenic interferes with normal metabolism. This is also shown by the fact that Chittenden and Cummins[8] and others found that it reduced the excretion of carbon dioxide.

The physiological action of thyroidase being to enhance catabolism both by stimulating the test-organ and the adrenal center, arsenic, as the antagonist of thyroidase, opposes catabolism, *i.e.*, a too rapid consumption of the cellular elements.[*] While, therefore, thyroid extract in sufficient doses causes emaciation, as shown by its action in obesity, arsenic provokes the opposite effect, gain in flesh.

The general effects of arsenic on nutrition are illustrated by the use to which the peasants of Styria, Tyrol and Lower Austria put it—the men to increase their physical activities, the women to enhance their charms, round off their shape, clear their complexion, etc. Their habitual use of the drug, however, engenders tolerance, *i.e.*, habituation of the adrenal center to its presence in the blood,[*] and increasingly large doses becomes necessary to obtain the desired effects. They thus become "arsenic-eaters." As shown by Cloetta, however, much of the arsenic ingested is not absorbed, but passes out with the fæces.

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[*] *Author's conclusion.*

[2] Besredka: Ann. de l'Inst. Pasteur, T. xiii, pp. 49, 209, 1899.

[3] Gautier: Trans. 13th Inter. Med. Congress, Sect. Gen. and Exp. Pathol., p. 545, 1900.

[4] Bédart and Mabille: C. r. de la Soc. de biol., 10 série, T. v, p. 556, 1898.

[5] Ewald: Die Therap. d. Gegenwart, Sept., 1899.

[6] Hutchison: Brit. Med. Jour., July 16, 1898.

[7] Lauder Brunton: Lancet, May 4, 1901.

[8] Chittenden and Cummins: Studies Lab. of Physiol. Chem., Yale Univ., vol. ii, p. 200, 1887.

Knapp[9] has witnessed, and brought before a medical meeting a peasant who took in their presence, without apparent discomfort, 0.33 gm. (5 grains) of arsenous acid. This does not seem to influence the mortality of Styrian peasants, who, in fact, live to old age. Gies[10] found that fowl could also be made to ingest large doses, if gradually habituated to the drug. He also administered minute doses to some young rabbits several weeks, leaving others of the same litter untreated. The treated animals became larger than the controls, the muscles, bones, and fat being better developed. Others have made similar observations. Stockman and Greig,[11] however, noted only an increase in the size of the bones. It is well known, however, that animals given arsenic, lay on fat. Lardelli[12] confirmed this observation experimentally, but he found also that the increase in weight was due, "in great part," to the nitrogenous constituents.

In skin disorders, arsenic is beneficial because, by reducing the metabolic activity in the muscularis of arteries it causes, in small therapeutic doses, slight general vasodilation.* As the caliber of the cutaneous arterioles is likewise increased, the capillaries of the skin, among others, receive a greater influx of auto-antitoxin-laden arterial blood. This serves not only to free mechanically the cutaneous intercellular spaces of toxic wastes, cellular débris and other pathogenic substances that may be present, but also to hasten their destruction and insure their freer transmission to the general blood-stream where they are finally broken down and thus converted into benign and eliminable excretory products.*

The physiological action of arsenic thus interpreted, indicates that it should not be used when the cutaneous disorder present is attended with acute inflammation; the greater influx of blood in the capillaries of the skin cannot but aggravate such a condition and the disease itself.

This coincides with the clinical results recorded by dermatologists. Many have found arsenic harmful during the earlier stages of cell proliferation. Duhring, for instance, states that "it should not be prescribed where there is great heat, burning, intense itching, or rapid cell-change. It is not only of no benefit at this stage, but in most cases it is positively injurious, tending to augment the activity of the morbid process." Brocq[13] emphasizes the importance of avoiding its use in the forms of eczema and other disorders attended by the least inflammatory phenomenon. Shoemaker[14] deems it valuable only in the absence of irritation and inflammation. In chronic, sluggish processes, however, it is of great value.

The vasodilation produced is well shown by the fact that even therapeutic doses will cause, as is well known, œdema, *i.e.*, effusion of blood-serum through the walls of the capillaries.

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* *Author's conclusion.*

[9] Knapp: Manquat: *Loc. cit.*, vol. i, p. 934.

[10] Gies: Arch. f. exper. Path. u. Pharm., Bd. viii, S. 175, 1877.

[11] Stockman and Greig: Jour. of Physiol., vol. xxiii, p. 376, 1898.

[12] Lardelli: Münch. med. Woch., Bd. liii, S. 2288, 1906.

[13] Brocq: "Traité d. mal. de la Peau," 1890.

[14] Shoemaker: "Mat. Med. and Therap.," fifth edition, 1901.

Untoward Effects.—When therapeutic doses are proving toxic, the cutaneous capillaries become overburdened with blood,* serous effusion into the connective tissue occurs, and œdema appears, at first under the eyes, then elsewhere.

The morbid effects of salvarsan (dioxydiamidoarsenobenzol), as described by Hoffman, Jaffé and Moirowsky, blue-red swelling of the face, lips and eyes, dyspnœa, severe diarrhœa and anuria, death being threatened,[14a] illustrate the paresis of the sympathetic control over the arterioles. This is further proven by the fact that, as first shown by Milian of Paris, the free use of adrenal, which, as is well known, contracts these arterioles, counteracts the morbid effects of salvarsan.

Chronic Poisoning.—The chronic form of arsenic poisoning, due to the absorption of very small particles from wall-paper, arsenical paints, stuffed animals, factories, mines, beverages, etc., illustrates the gradual development of lesions incident upon lowered general metabolism. Increasing weakness, gastric dilation, headache, lachrymation, congestion of the conjunctiva, coryza, sneezing, cough, cardiac dilation, enlargement of the liver, swelling beneath the eyes or of the face and extremities, all point to a general relaxation of the muscles, including those of the cardiovascular system. Imperfect cleavage of toxic wastes causes the appearance of eruptions of various kinds, some attended by intense itching. Bronzing is often witnessed in these cases, the skin falling off in brownish scales or in large flakes. Pallor and slight cyanosis may be observed.

Nervous disorders appear in practically all cases—sensory affections especially, varying from slight paræsthesia to complete anæsthesia due to imperfect oxygenation of the peripheral end-organs, to intense headache, neuralgia, muscular tenderness, pains in the joints, formication of the lower extremities, and perversions of the temperature sense. Erythromelalgia, *i.e.*, swelling, redness, and hyperæsthesia of the palms and soles, may also appear. Motor paralyses are met with in a large proportion of cases, in the lower extremities especially, recalling locomotor ataxia, and are often preceded by the sensory phenomena. They usually begin in the toes or fingers and are generally symmetrical. The knee-jerks may be exaggerated early in the history of a case, but when paralysis and atrophy appear, they are absent. Prolonged intoxication has given rise to insanity and epilepsy, and to a state of mental torpor simulating idiocy.

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* *Author's conclusion.*

[14a] Ehrlich: British Medical Journal, May 9, 1914.

All these morbid phenomena gradually disappear when the patient is no longer exposed to the effects of the poison and judiciously treated, provided disintegration of the muscular tissue has not occurred.

The pathology of chronic arsenic poisoning, as stated by Cushny, is "still obscure," but its nature—in the light of the foregoing analysis—is plainly suggested in view of the fact that, as observed by Wood,[15] "a peculiar brown pigmentation of the skin," *i.e.*, a light bronzing, "is almost pathognomonic of chronic arsenicalism." This pigmentation may even be generalized as shown by a case reported by J. Sobel,[16] some regions, the anterior and posterior surfaces of the neck, the inner sides of the thighs, etc., being "dark brown." Arsenic inhibits the functions of the adrenal system, and causes general vasodilation.

The lesions found in the spinal cord are usually ascribed to a "neuritis," a "myelitis," or the cord is said to be "inflamed." When, however, we consider that these conditions are said to be observed immediately after death from acute experimental poisoning, it becomes evident, in view of the data just submitted, that the condition present is misunderstood. What we see under these conditions is not an "inflamed" cord but an organ the vessels of which are dilated precisely as they are throughout the entire body.* In more protracted cases the vessels are said to be surrounded by an "exudation" ascribed to a so-called "inflammatory process;" but we are obviously dealing with an accumulation of blood-fluids. The walls of the vessels are said to be "thickened" and the cellular nervous elements "degenerated," but these are merely morphological alterations due to engorgement of the vasa vasorum and of the cellular elements themselves, including the multipolar cells, due to the one morbid effect of the drug: general vasodilation. Even the widespread "fatty degeneration" so-called is naught else, as we have seen in the first volume, but blood-serum converted into myosin. Wonder is expressed in text-books that in practically all cases, whether due to acute or chronic poisoning and even in paralytics showing the "reactions of degeneration," recovery occurs after discontinuing the use of the drug. This result becomes a normal one, however, when absorption of extravasated fluid devoid of physiological value and resumption of vascular tone are taken into account.

Acute Poisoning.—Arsenic, *i.e.*, arsenous acid, when in contact with the fluids of living tissues, *i.e.*, the blood-serum, becomes converted into arsenic acid, owing to the presence of the oxygen-laden adrenoxidase in these fluids.* Therapeutic doses of arsenic on reaching the stomach become, therefore, markedly active and may excite gastro-intestinal irritation.

Adrenoxidase is a constituent, we have seen, of the blood-serum, and therefore of the various secretions. Binz and Schulz[17] found that albumin, fibrin and blood could convert arsenous to arsenic acid, and *vice versa*, the brain, liver, pancreas and kidney exercising marked activity in this process, and fats none. Cushny[18] also deems it probable "that the oxides of arsenic alone are capable of modifying vital functions." The avidity of arsenic for oxygen is satisfied as soon as it reaches the oxygen-laden fluids and tissues, and the violent abstraction of this gas from the latter accounts for its corrosive action.

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* *Author's conclusion.*

[15] Wood: *Loc. cit.*, p. 451, eleventh edition, 1900.

[16] J. Sobel: Archives of Pediatrics, Jan., 1907.

[17] Binz and Schulz: Arch. f. exper. Path. u. Pharm., Bde. xi, S. 208, 1879; xiv, S. 345, 1881; xxxvi, S. 275, 1895.

It is owing to the presence of adrenoxidase in the fluids of the entire alimentary canal that a poisonous dose of arsenic may cause severe pain in the throat, œsophagus, stomach, and abdomen, nausea and vomiting, and organic lesions, *i.e.*, congestion, ecchymoses, erosions attended sometimes by hæmorrhages.* Purging is likewise the result, though only in part, of the violent intestinal irritation. Although the discharges may be merely loose, greenish, or yellow, they often assume the aspect of the rice-water stools of Asiatic cholera, and contain minute flakes of mucous membrane. The excessive loss of fluid may then entail diminution or suppression of urine.

The general or secondary effects of the poison are of another order. Arsenic is readily absorbed and the functional activity of the adrenal center is soon depressed and finally inhibited. Owing to the more or less advanced adrenal insufficiency thus engendered, the heart's action and the pulse become weak and small, and because of the marked general vasodilation, very rapid. The respirations are painful, labored, and frequent—an effort to compensate for the paucity of adrenal secretion available. As a result of the diminution of adrenoxidase in the blood and tissues the temperature gradually recedes, the extremities and body become very cold—recalling, with the concomitant symptoms, cramps, etc., the algid stage of cholera. Gradually as the blood loses its oxygenizing properties, the surface becomes dark and cyanosed, coma, and sometimes convulsions, supervene, and death ends the patient's intense suffering.

The functions of the adrenal center are evidently inhibited. Thus, arsenic may, as we have seen, provoke the characteristic symptoms of Addison's disease—progressive wasting, asthenia, hypothermia, general vasodilation, etc., including the characteristic pigmentation, *i.e.*, *bronzing*—all of which often disappear when the use of arsenic is discontinued. The case of Enriquez and Lereboullet,[19] Hutchinson,[20] Förster,[21]

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* *Author's conclusion.*

[18] Cushny: *Loc. cit.*, p. 616, fourth edition, 1906.

[19] Enriquez and Lereboullet: Gaz. hebd. de méd. et de chir., July 6, 1899.

[20] Hutchinson: Arch. of Surg., vol. v, p. 329, 1894.

[21] Förster: Berl. klin. Woch., Bd. xxvii, S. 1150, 1890.

Richardière,[32] Heuss,[33] Leszynsky,[34] and many others reported, afford evidence to this effect.

Subserous ecchymoses in the endocardium, confined to the left ventricle in eight out of ten cases of acute arsenical poisoning, was observed by Powell,[35] police surgeon in Bombay.

Moreover, arsenic, by causing ischæmia of the pituitary, deprives it of its reflex activity.*

Boehm and Unterberger[36] found that both the *sensory* and *motor* paths of the upper spinal cord failed to cause the usual vasoconstriction. Such was also the case after Cyon and Massolongo had removed the pituitary body. This cannot be due to inability of the paths themselves or of the muscular coats of the arteries (owing to inhibition of their metabolism) to react under the influence of the stimulus, since the authors found that the arteries of the ear of the same animals were still constricted sufficiently to cause pallor when the cervical sympathetic was stimulated. Hence, we are dealing with a central paralysis, in accord with the prevailing view among therapeutists—but of a center located in the pituitary body, that of the adrenals. Pistorius[37] recently argued that it was the vasomotor center which lost it control over vessels, but as shown by Boehm and Unterberger, arsenic is first of all a respiratory poison—a view sustained by the marked inhibitory effect of arsenic on oxygenation, a process governed by the adrenal center, *i.e.*, the thermic center.*

After large doses, collapse and death may occur suddenly within twenty-four hours, the case lapsing almost from the start into the advanced stage. When the quantity ingested is not great, or when a part of it has been eliminated by vomiting, the primary symptoms may cease and the patient apparently improve. In many instances, however, this is only temporary; a recrudescence of the symptoms occurs, more intense perhaps than the first, but often accompanied (as a result of the corrosive action of the poison on the alimentary canal) by fever, a dry tongue, and considerable tumefaction of the abdomen. Eruptions, which may be pustular, papular, vesicular, or petechial, are often witnessed in these cases. The algidity, the intense dyspnœa, cyanosis, muscular trembling, cramps, and other characteristic symptoms of a primary acute attack nevertheless prevail and death may take place between the second and sixth day.

Recovery in such cases is slow and is usually attended by disorders of various types: of the stomach and intestines owing to the local lesions; of the nervous system or of limited portions thereof, sensory or motor, due mainly to trophic changes during the whole process; of the liver and kidneys owing to excess of toxic substances in the blood, etc.

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* *Author's conclusion.*

[32] Richardière: Ann. d. derm. et syphil., 3 série, T. v, p. 1296, 1894.

[33] Heuss: Corr. f. schweitz. Aerzte, Bd. xxiv, S. 301, 1894.

[34] Leszynsky: N. Y. Med. Jour., Mar. 23, 1899.

[35] Powell: Bombay Med. and Phys. Soc., vol. ix, 1905.

[36] Boehm and Unterberger: Arch. f. exp. Path. u. Pharm., Bd. ii, S. 89, 1874.

[37] Pistorius: Arch. f. exp. Path. u. Pharm., Bd. xvi, S. 188, 1882.

In the epidemic of arsenical poisoning which occurred in Manchester a few years ago among beer-drinkers, E. S. Reynolds[illegible] found a large number of cases of peripheral neuritis, especially among women. In many of the cases the skin of the armpits, the nipples and the genital organs "was deeply pigmented, as in Addison's disease." Out of a series of 253 cases of neuritis collected by W. Janowski,[illegible] 136 were found to be due to acute arsenical poisoning. As observed by Boehm and Unterberger, and Pistorius, in poisoned animals even such large trunks as the splanchnic, which at first transmitted impulses, failed to do so later on. Impaired metabolism in their structure is a normal result of adrenal insufficiency caused by arsenic. It is, in fact, the main initial feature of the post-acute nervous disorders, when all nervous elements are regarded as channels for oxygen-laden blood-plasma.*

The *treatment of arsenic poisoning* is described in a special section at the end of this volume.

Therapeutics.—The manner in which arsenic produces its beneficial effects in certain *skin diseases* was explained on page 1302. It has proven equally efficacious in *pernicious anæmia*, a disorder due, as will be shown elsewhere, to hæmolysis through excess of auto-antitoxin and adrenoxidase in the blood.* By reducing the activity of the adrenal center and the production of adrenoxidase, arsenic counteracts this morbid phenomenon.* It is also a specific in *chorea,* another disorder due to excessive metabolic activity resulting in uncontrollable muscular activity.* In *diabetes,* the manner in which arsenic produces its beneficial effects is almost self-evident: we have seen that this disorder is due to excessive activity of the anterior pituitary, manifested through the test-organ and the adrenal center;* arsenic by depressing the activity of the adrenal center* counteracts the morbid process. In *torpid catarrhal processes,* chronic rhinitis, chronic gastritis, etc., and in persons who readily "take cold" and whose extremities are usually hypothermic, arsenic is also of value. owing to its action on the arterioles of the mucous membrane and skin. The excess of the arterial blood admitted into the capillaries enhances the curative process by introducing an excess of auto-antitoxin in the diseased tissues, and relieves the superficial hypothermia and tendency to "colds" in debilitated individuals.* It is also because the cutaneous hyperæmia thus produced insures an increased supply of auto-antitoxin in the superficial tissues* that arsenic, as stated in the first volume,[30] protects the body against *malaria, and other diseases* in which the pathogenic agent is introduced into the blood by the sting or bite of insects, infection under these conditions depending upon the antitoxic activity of the cutaneous blood.* The curative action of arsenic in *intermittent fever* is likewise due to the accumulation of auto-antitoxin in the cutaneous capillaries*—the minute channels which Nature utilizes as a powerful adjunct to the liver when an exacerbation of defensive activity, "fever," becomes necessary.*

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* *Author's conclusion.*
[illegible] E. S. Reynolds: Brit. Med. Jour., Nov. 24, 1900.
[illegible] W. Janowski: Zeit. f. klin. Med., Bd. xlvi, S. 60, 1902.

CHLORAL.

Physiological Action.—Chloral causes sleep by depressing directly the functional activity of the test-organ and, through it, of the adrenal center. The quantity of adrenal secretion produced being diminished, less adrenoxidase is formed and the metabolic processes in general become less active.* The brain, owing to the great volume of blood it contains, is one of the first organs to feel the influence of lowered oxygenation; the gemmules of its cellular elements are retracted and comparatively normal sleep is produced when the dose is not excessive.* The respirations, the cardiac action and the pulse are somewhat slowed and the temperature is slightly lowered, but on awakening from four to eight hours after ingesting the dose, the patient feels about as usual, though perhaps a little weary and confused.

That chloral is absorbed unchanged in the blood and circulates as such is now generally recognized. Liebreich's view, that it is split into chloroform and sodium formiate, has been shown by Labbée,[31] Tomascewicz[32] and others to be erroneous. It is not, however, by a direct action on the blood itself that it acts, for Rajewsky[33] found that the drug produced its typical effects on a frog whose blood had been replaced by salt solution. Nor is it by a direct action on the motor nerves, for the same investigator and Labbée found that even fatal doses had no influence on these structures. Both these investigators traced the phenomena witnessed to the spinal centers.

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* *Author's conclusion.*

[30] *Cf.* vol. i, p. 769.

[31] Labbée: Arch. gén. de méd., vol. xvi, p. 330, 1870.

[32] Tomascewicz: Arch. f. d. ges. Physiol., Bd. ix, S. 35, 1874.

[33] Rajewsky: Centralbl. f. d. med. Wissen., Bd. viii, S. 211, 1870.

The prevailing view is that chloral paralyzes the respiratory center. Although, as observed by Loewy,[34] there is practically no difference between normal sleep and the effect of a therapeutic dose in this particular, Cushny[35] states that "as the dose is increased . . . . . , the respiration becomes very slow and weak, and finally ceases from paralysis of the center." Even therapeutic doses, as observed by DaCosta[36] and others, reduce the temperature. When the doses are large, this reduction may become very marked. Thus, B. Ward Richardson[37] observed a reduction of 10.8° F. (6° C.) in the rabbit. Hammarsten[38] obtained a similar reduction in one hour, "though the animals were well wrapped up and laid in a warm place." This is evidently due to deficiency of oxygen-absorbing power of the blood, for the air utilized is considerably reduced. Thus Wood and Cerna[39] found experimentally that the reduction in the amount of inspired air produced by large doses was, in many instances, 50 per cent., and that sometimes it amounted to 75 per cent. These experiments demonstrated, in their opinion, that in the dog, chloral was a true respiratory depressant. Again, the effects of chloral in man being similar to those exerted upon the dog, they conclude that in human beings chloral likewise paralyzes the respiratory centers. H. W. Mitchell[40] refers to a case in which the oxygenation of the blood was sufficiently impaired to produce cyanosis. Wood concludes,[41] in view of Rajewsky's experiments, that "the influence of chloral must be exerted upon the respiratory center at the *base* of the brain." All these observations harmonize with those of Richet,[42] who found that chloral greatly reduced the excretion of carbon dioxide, and with those of Germain Sée[43] and others, who ascribe to chloral a paralyzing action on the "thermic centers"—also thought to be at the *base* of the brain. As I have pointed out,[44] the thermic center is the adrenal center.

As the paralysis of the adrenal center becomes more marked gradually as the dose is increased, the oxygenization of the tissues is correspondingly lowered and the functional activity of all organs, including the muscular layer in the walls of the vessels and the cardiac muscle, is lowered in proportion.* General vasodilation occurs as a normal result.* This feature of the action of chloral renders the use of large doses dangerous.

Large therapeutic doses, by augmenting the adrenal insufficiency and causing marked general vasodilation,* produce a deep sleep which lasts twelve to eighteen hours, and from which the patient can only be awakened with considerable difficulty. All functions being to a certain extent impaired by the paucity of adrenoxidase in the blood,* the respirations are reduced, the pulse becomes weak, and reflex activity is markedly diminished. The reduction of the blood circulating in the cutaneous capillaries, supplemented by the deficient oxygenizing power of the blood, not only gives rise to partial anæsthesia of the surface, but also to a great reduction of the peripheral temperature. The awakening after such a dose is often attended with marked evidence of general disturbance; *i.e.*, mental torpor, confusion, headache and sometimes nausea and vomiting.

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* *Author's conclusion.*

[34] Loewy: Pflüger's Arch., Bd. xlvii, S. 601, 1890.

[35] Cushny: *Loc. cit.*, p. 188, fourth edition, 1906.

[36] DaCosta: Cited by Wood: *Loc. cit.*, p. 149, thirteenth edition, 1906.

[37] B. Ward Richardson: Med. Times and Register, Sept. 4, 1869.

[38] Hammarsten: Cited by Wood: *Loc. cit.*, p. 149, thirteenth edition, 1906.

[39] Wood and Cerna: Jour. of Physiol., vol. xiii, p. 870, 1892.

[40] H. W. Mitchell: Boston Med. and Surg. Jour., Jan. 31, 1907.

[41] Wood: *Loc. cit.*, p. 149, thirteenth edition, 1906.

[42] Richet: Arch. de Physiol. norm. et path., 5 série, T. ii, p. 221, 1890.

[43] Germain Sée: C. r. de l'Acad. de méd., July 22, 1880.

[44] *Cf.* this volume, p. 1006.

General vasodilation is a well-known feature of the action of chloral. Demarquay[45] long ago observed that it caused in animals, not only vasodilation, but also engorgement of all vessels. Kobert[46] was led experimentally to conclude that it caused paralysis of the vascular walls. As Labbée and other investigators noted that the rabbit's ear grew pale after its use, the general vasodilation had evidently caused recession of the blood into the great central trunks, thus tending to deplete the brain and the peripheral capillaries. This accounts, with the lowered oxygenizing power of the blood, for the fact, mentioned by Cushny,[47] that "the motor areas are rendered less irritable by chloral, and eventually fail to react to the strongest electrical stimulation." It also explains the mental torpor and the partial anæsthesi Even relatively small doses will cause relaxation of the arteries as observed by Labbée. Rajewsky, moreover, observed that small, as well as large, doses reduced the blood-pressure.

In some instances, a therapeutic dose causes flushing of the face, hyperæsthesia, restlessness, excitement and even delirium with hallucinations. This effect is due to the relaxation of the arterioles.* A greater quantity of arterial blood being admitted into the cutaneous and cerebral capillaries than usual,* a period of morbid activity follows.

Arloing found not only that the small vessels were dilated but that the supply of blood in the peripheral tissues was increased. This condition doubtless prevails in the deeper organs, including the cord, for Rajewsky[48] observed reflex irritability in frogs and that at this time the spinal ganglia were overexcitable. Moreover, Levinstein[49] observed a rise of temperature followed by marked fall. Some investigators, having noted sphygmographically an increase in size of the limb immersed, concluded that chloral increased the arterial pressure. But a similar effect is produced when the peripheral capillaries are dilated passively by unusual dilation of their arterioles. Cerna, working in Wood's laboratory, found it impossible to raise the blood-pressure in curarized dogs, with any dose of chloral. Even with the sphygmograph, Preisendörfer[50] found that the supposed period of preliminary rise was followed by a steady decline of blood-pressure, while Andrews and DaCosta[51] ascertained that very large doses "decidedly lessen arterial pressure."[52]

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* *Author's conclusion.*

[45] Demarquay: Bull. gén. de thérap., méd. et chir., T. lxxvii, p. 307, 1869.

[46] Kobert: Therap. Gaz., Jan. 15, Feb. 15, June 15, 1887.

[47] Cushny: *Loc. cit.*, p. 187, fourth edition, 1906.

[48] Rajewsky: Centralbl. f. med. Wissen., Bd. viii, S. 261, 1870.

[49] Levinstein: Lancet, Feb. 21, 1874.

[50] Preisendörfer: Deut. Archiv f. klin. Med., Bd. xxv, S. 48, 1880.

A toxic dose tends to paralyze the adrenal center and to arrest therefore the functions of the adrenals, and the formation of *adrenoxidase.** It tends to kill, therefore, by paralyzing the respiratory function.* The patient sinks into a profound sleep from which it is practically impossible to awaken him, the skin, owing to the morbid condition of the blood, being absolutely insensible. The pupils are widely dilated and the muscles are completely relaxed. The heart having lost the sustaining aid of the adrenal secretion and being nourished with blood deprived of its main constituent,* becomes steadily weaker and more irregular, the pulse presenting the same character. The temperature steadily declines and the respirations become gradually slower and irregular until they cease, death occurring from asphyxia. The heart continues to beat a short time, stopping in diastole. Occasionally, however, respiration and cardiac action cease together.

The diminution of adrenal secretion, *i.e.*, adrenoxidase, being the cardinal factor of the morbid process, it becomes a question whether chloral actually reduces its production. B. Ward Richardson[53] found that this drug reduced the coagulability of the blood—a morbid phenomenon due, we have seen, to diminution of fibrin ferment. As previously shown, this body is adrenoxidase.* Now Model[54] observed that chloral predisposed to hæmorrhage—a phenomena due to reduced coagulability of the blood—while, on the other hand, Duncanson[55] and Lange[56] found that adrenal extract (which becomes adrenoxidase in the blood) controlled the hæmorrhages of hæmophilia, a condition due to deficiency of fibrin-ferment.

Again, we have seen, that removal of the adrenals or ligation of their efferent vessels causes a rapid reduction of the blood-pressure and of the temperature, ending in death, the characteristic phenomena of chloral poisoning. This is surely due to the fact that the blood is deprived of the adrenal secretion, for Strehl and Weiss,[57] after removing one adrenal, found that they could control the temperature and the blood-pressure at will by pinching and releasing the efferent vessels of the remaining adrenal. Now, when chloral has brought an animal to the verge of death, adrenal extract immediately counteracts the lethal condition. Gottlieb[58] "chloralized rabbits until the heart beats became irregular and excessively slow. An injection of suprarenal extract at once restored the regularity and volume of the pulse. He tried the same

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* *Author's conclusion.*
[51] DaCosta: Amer. Jour. Med. Sci., Apr., 1870.
[52] Cited by Wood: *Loc. cit.*, p. 148, thirteenth edition, 1906.
[53] B. Ward Richardson: *Loc. cit.*
[54] Model: Münch. med. Wochen., Bd. xlvii, S. 1729, 1900.
[55] Duncanson: Brit. Med. Jour., Feb. 21, 1902.
[56] Lange: Münch. med. Woch., Bd. l, S. 62, 1903.
[57] Strehl and Weiss: Arch. f. d. ges. Physiol., Bd. lxxxvi, S. 107, 1901.
[58] Gottlieb: Arch. f. exp. Path. u. Pharm., Bd. xxxviii, S. 99, 1896.

experiment when the pulse was no longer registrable by the manometer; a similar result was obtained, and the heart almost immediately resumed its normal action." Here the adrenal secretion became converted into adrenoxidase and thus supplied the blood for a short time with its *pabulum vitæ*—in lieu of the animal's own adrenals, inhibited through paralysis of its center by the poison.

Chronic Poisoning.—The prolonged use of chloral hydrate provokes phenomena due to continued depression of the adrenal center, lowered metabolism, and the resulting general vasodilation.*

Respiratory disorders are frequently observed. The most prominent symptom is dyspnœa due to the diminution of adrenoxidase in the blood.* This may be severe and even alarming when the general vasodilation becomes sufficient to slow the circulation, and when the right heart, owing to the inadequate supply of adrenal secretion and adrenoxidase,* becomes feeble. The dilated capillaries allowing the blood fluids to traverse their walls with unusual facility, œdema may occur into the mucous membranes, skin, or deeper organs. *Mental disorders* are also witnessed in some cases in the form of intellectual torpor, loss of memory, or impulsive illusions and hallucinations due to fluctuations in the caliber of the vessels and the quantity of blood supplied to the brain. If the use of the drug be stopped suddenly, the vasomotor nerves soon resume the ascendency over the vessels, and the brain, receiving an influx of blood containing a greater supply of adrenoxidase, becomes overactive. Manifestations resembling delirium tremens may appear under such conditions. *Cutaneous disorders* are frequently observed. These are mainly due to the accumulation of wastes in the blood, owing to its reduced catabolic activity, and to the reduced propulsive vigor of the blood-stream which the vasodilation involves. They may assume the form of erythema, ecchymoses, petechiæ, or of ephemeral red patches, either in the skin or mucous membranes. The lesions sometimes cause considerable trouble, however. ulceration, fever and pyæmic toxæmia.

H. W. Mitchell[88] reported an interesting case which, as he says, "illustrates the resemblance between alcohol and chloral delirium." The mental disorder became so marked that the patient had to be placed in an asylum. Withdrawal of the drug, stimulation, forced feeding, hydrotherapeutic measures, with a hypnotic the first three nights, were followed by complete recovery. The author refers to Elliott,[**] who states that "there was no appreciable difference in delirium tremens resulting from the use of alcohol or chloral."

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* *Author's conclusion.*

[88] W. H. Mitchell: *Loc. cit.*

The *treatment of chloral poisoning* is described in a special section at the end of this volume.

Therapeutics.—Chloral is mainly used in *insomnia*, especially when associated with nervous irritability. Its great value in this connection is due to the fact that by lowering metabolic activity it depresses the functions of all cellular elements including those of the nervous system, in which, we have seen, adrenoxidase likewise circulates.[*] The slight fall of blood-pressure which the lowered metabolism in the muscularis of the vessels causes when therapeutic doses are given, promotes ischæmia of the cerebro-spinal system and facilitates the soporific effects.[*] Its influence on pain (which is due to hyperæmia of the sensory terminals[*]) is slight, however, because the dilation of the arterioles caused by the remedy allows an excess of blood to penetrate the capillaries, thus offsetting what analgesic effect the lowered metabolism in the cellular elements might otherwise procure.[*] The recognized value of chloral in *chorea, paralysis agitans* and *uræmic convulsions* as a palliative is also due to its depressing influence on the vital and vascular mechanism,[*] which in these conditions are both overactive.[*] This applies as well to *puerperal eclampsia, epilepsy, hydrophobia* and *infantile convulsions,* in all of which chloral is frequently used; but it should be remembered that it is by no means a curative remedy[*] and that it tends, like all depressants, to promote the formation of the toxic wastes which act as spasmogenic agents.[*]

DRUGS WHICH RESEMBLE CHLORAL IN THEIR PHYSIOLOGICAL ACTION.

Paraldehyde acts much as does chloral. It primarily lowers the functional activity of the adrenal center, and by thus indirectly reducing the proportion of adrenoxidase in the blood, correspondingly inhibits metabolism in all tissues. As a result the muscular layer of the vessels is relaxed and general vasodilation, though not so marked as in the case of chloral, follows.

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[*] *Author's conclusion.*

[**] Elliott: Lancet, May 24, 1873.

The sleep produced by therapeutic doses usually comes on within five minutes. It is not attended by anæsthesia, but resembles that caused by chloral, being calm and restful, and usually lasts five or six hours. It is likewise due to diminished metabolic activity in the cerebral nervous elements, and its effects are more marked in normal than febrile subjects. Occasionally, especially in the latter, it provokes unpleasant dreams and nightmares, and flushing, owing to a slight dilation of the arterioles and the admission in the cerebral and peripheral capillaries of a slight excess of arterial blood over that compatible with normal sleep. As a rule, the awakening is not followed by untoward symptoms; at times, however, depression, mental torpor, and lack of energy are complained of.

A *toxic dose* produces general muscular relaxation and unconsciousness and, sometimes, cyanosis. The cardiac contractions and the pulse become gradually weaker and intermittent. The respirations, at first rapid, soon become shallow and irregular, and death occurs from asphyxia. The symptoms that appear in paraldehyde habitués are similar to those observed in the chronic form of chloral poisoning, and likewise include emaciation, great muscular and cardiac weakness, and mental disorders. These are sufficiently severe in some cases, that it becomes necessary to place the patient under restraint.

Sulphonal.—Besides lowering the functional activity of the adrenal center,* sulphonal tends to decompose the hæmoglobin, as shown by the many cases in which hæmatoporphyrin, *i.e.*, iron-free hæmatin, is found in the urine. Any drug capable of such an action cannot but undermine the health. Preference should be given, therefore, to chloral or paraldehyde.

In therapeutic doses sulphonal produces apparently normal sleep of several hours' duration, from which he may awaken in his usual condition. Not infrequently, however, he experiences mental torpor, some lassitude, and perhaps vertigo. If the use of the drug is prolonged, it may give rise to general weakness, principally of the lower extremities, and sometimes to faintness, nausea, vomiting and serous diarrhœa. When large doses are used, the foregoing symptoms may more or less suddenly be accompanied by more serious ones. Respiratory phenomena, the salient features in acute cases, then appear: the face and body become cold and livid, the lips and nails cyanosed, the respirations reduced in number and shallow, and the heart's action feeble and intermittent.

In *acute poisoning* met with in subjects addicted to the drug or others to whom it has been administered some time, premonitory symptoms, such as colic about the epigastrium, vomiting, diarrhœa, or obstinate constipation, a papular eruption and marked weakness, may appear; but such is seldom the case in neurasthenics. In these, which constitute the majority of cases, the acute symptoms usually appear suddenly and terminate fatally.

Trional.—Trional, which is very similar to sulphonal chemically, resembles it also in its physiological effects. Its depressing action upon the adrenal center is more marked,* however, while its dissociating effect upon the hæmoglobin is probably less active. It is,. therefore, somewhat more powerful as an hypnotic, and when acute symptoms of poisoning occur, the chances of recovery are greater, and are not as likely to appear after one or two doses. The majority of cases of poisoning occur in persons who have taken the drug some time.

The symptoms due to *toxic doses* are often initiated by colic, persistent nausea and vomiting, and diarrhœa, owing to a sudden relaxation of the vessels and outpouring of blood-fluids into the alimentary canal. This is usually followed by obstinate constipation due to paresis of the intestinal muscles—a paresis witnessed in various parts of the body, particularly the extremities. The heart's action and the pulse now become very weak and rapid, and dilation murmurs are sometimes discernible over the mitral and aortic valve-signs—signs of impending heart-failure.' Respiratory disturbances occur concomitantly; the lips and nails may become cyanosed and the patient lapses into coma. Death occurs most frequently in cases in which hæmatoporphyrin is found in the urine. But large quantities of urobilin and bilirubin are still worse as prognostic signs, since they indicate that the disintegration of hæmoglobin has reached its most advanced stage.

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* *Author's conclusion.*

ALCOHOL.

Physiological Action.—The effects of alcohol upon the alimentary canal vary with the proportion contained in the ingesta. When the latter contain less than five per cent. of absolute alcohol, the secretory activity of the salivary gastric glands is increased reflexly and the digestive process is either stimulated and facilitated, or unimpaired. When 5 per cent. is exceeded, the digestion may be delayed. A beverage containing 10 per cent. of absolute alcohol and above, interferes with the digestive process in proportion as the percentage is high, by inhibiting the diastatic and proteolytic activity of the gastric juice.

All experimental data recited below refer to *beverages containing more than 5 per cent. of absolute alcohol.*

The experiments of Buchner,[61] Chittenden and Mendel,[62] Storck[63] and others, have shown that when there is not more than five per cent. of absolute alcohol in the beverages ingested, the salivary digestion is enhanced, but that a higher proportion of alcohol tends to delay the process, especially when it exceeds 10 per cent. Chittenden, Mendel and Jackson[64] ascribe the increased flow of saliva to reflex action, provoked by the irritation of the alcohol on the oral nerve endings.

Gastric digestion is correspondingly influenced. The stimulating action of small quantites of alcohol is emphasized by the observation of Nothnagel and Rossbach[65] that a single drop injected into the stomach of a dog, through a gastric fistula, suffices to provoke a flow of gastric juice through the cannula. Chittenden, Mendel and Jackson, Radzikowski[66] and others also found that alcohol in moderate doses markedly increased the secretion of gastric juice, its proteolytic activity and the proportion of hydrochloric acid. Richet[67] likewise observed that it increased the acidity of the gastric juice. Similar effects are obtained, as shown by Froum, Moulinier, and Spiro,[68] when alcohol is administered by enema and when, as observed by Grénet,[69] it is injected into the blood. Elliston[70] found, moreover, that after the ingestion of small doses the increased secretion of gastric juice continued much longer than when none had been administered.

The pernicious influence of a large percentage of alcohol in the ingesta is no less evident. Claude Bernard has shown that strong doses of alcohol coagulate the gastric secretion and its ferments. Gluzinski[71] found that they impaired the digestion of albumins, the digestion being retarded. Two ounces of brandy taken before or during a meal, inhibit the digestion of starches. Taken after meals this quantity inhibits digestion. Lauren[72] found that it reduces the activity of pepsin on albumins. Thibault[73] noted that when the alcoholic strength exceeded 12.5 per cent. the proteolytic activity of the gastric juice was at once reduced. Chittenden and Mendel,[74] who also obtained stimulating effects from weak solutions, found that when the ingested mixture contains from 5 to 10 per cent. of absolute alcohol, retardation of the digestive process becomes noticeable, and that a 15 to 18 per cent. beverage retards it from 25 to 35 per cent.

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[61] Buchner: Deut. Archiv f. klin. Med., Bd. xxix, S. 537, 1881.

[62] Chittenden and Mendel: Amer. Jour. Med. Sci., Jan., Feb., Mar., Apr., 1896.

[63] Storck: N. O. Med. Jour., Dec., 1901.

[64] Chittenden, Mendel and Jackson: Amer. Jour. of Phys., Mar.; 1898.

[65] Nothnagel and Rossbach: "Mat. Med. et Therap.," Fr. edition, 1889.

[66] Radzikowski: Arch. f. d. ges. Physiol., Bd. lxxxiv, S. 513, 1901.

[67] Richet: Cited by Manquat: *Loc. cit.*, vol. ii, p. 652.

[68] Spiro: Münch. med., Woch., Bd. xlviii, S. 1871, 1901.

[69] Grénet: C. r. de la Soc. de biol., vol. iv, p. 376, 1902.

[70] Elliston: Med. Press and Circular, Sept. 16, 1891.

[71] Gluzinski: Cited by Manquat: *Loc. cit.*, vol. ii, p. 652.

[72] Lauren: Chem. Zeit. Rep., p. 312, 1893.

Alcohol having a marked affinity for oxygen, the harmlessness or beneficial effects of weak solutions, such as beer, is due to the fact that a small quantity of alcohol is promptly oxidized by the adrenoxidase of the oral, gastric and intestinal secretions.* The glandular elements, to compensate for the deficiency of adrenoxidase thus created, reflexly increase their functional activity.* The adrenals are also directly stimulated by small doses and, for a time, by large doses. When, however, the latter are continued, the adrenals become the seat, along with other endocrines, of degenerative lesions.

Bernard and Bigart[75] found that slight alcoholic intoxication increased the activity of the adrenals. Aubertin[76] observed experimentally that this was also caused by alcoholism with marked hyperplasia of the organs. Schmiergeld[77] confirmed this observation in man. Bernard and Bigart and Aubertin also observed in prolonged alcoholism fibrosis and evidences of hypoadrenia. Hirsch[78] found marked degenerative lesions in the adrenal cortices from cases of delirium tremens. Similar lesions have been observed in the thyroid by de Quervain,[79] Sarbach,[80] Hertoghe, and others.

When sufficient alcohol is taken to exceed the oxidizing powers of the secretions of the alimentary canal, the excess is absorbed into the general circulation and is oxidized therein by the adrenoxidase of the plasma and red corpuscles,* only about two per cent. being excreted in its natural state.

Liebig many years ago advanced the view that the greater part of the alcohol absorbed from the alimentary canal becomes oxidized in the body, and that but a very small quantity is eliminated by the lungs and kidneys. Anstie,[81] Thudicum and Dupré[82] in various experiments upon a large number of subjects found that the quantity of alcohol eliminated with the urine was trifling, *i.e.*, from 0.25 to 0.82 per cent.

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* *Author's conclusion.*

[73] Thibault: Jour. de pharm. et de chem., Feb. 15, 1902.

[74] Chittenden and Mendel: *Loc. cit.*

[75] Bernard and Bigart: Jour. de Pathol. et de physiol. gén., viii, 1014-1029, 1902.

[76] Aubertin: C. R. de la Soc. de Biol., Paris, lxiii, 270-272, 1907.

[77] Schmiergeld: Arch. de Méd. Experim. et d'Anat. Pathol., xxi, 75-86, 1909.

[78] Hirsch: Jour. Amer. Med. Assoc., lxiii, 2186, 1914.

[79] de Quervain: Semaine Méd., xxv, 517, 1905.

[80] Sarbach: Mitth. a. d. Grenzgeb. d. Med. u. Chir., xv, 212-246, 1905-1906.

[81] Anstie: "Stimulants and Narcotics," Phila., 1865.

[82] Thudicum and Dupré: Tenth Rep., of Med. officer of Privy Council, London, 1868.

Schulinus,[51] Buchheim[52] and Lieben[53] not only confirmed this fact, but found that while the elimination with the excretions was inappreciable during the two or three hours following its ingestion, 25 per cent. of the drug had disappeared from the blood and tissues. Greater precision was recently given to this question by the comprehensive researches of Atwater and Benedict,[54] which showed that in the adult man only 1.9 per cent. of the alcohol contained in six ounces of whiskey is eliminated. Abelous, Bardier and Ribaut[55] found that even when three c.c. per kilo of (warm-blooded) animal was given, 87 to 90 per cent. of the total ingested was destroyed within eight hours. Cushny[56] emphasizes the fact that the 5 to 10 per cent. generally thought to be eliminated "is too high a valuation for the alcohol excreted and that only 2 to 3 per cent. of that ingested escapes oxidation."

The loss of oxygen which alcohol imposes upon the tissues by undergoing oxidation in the blood-stream, interferes with general nutrition and, therefore, lowers the activity of the vital process when used in any but small quantities.

The utilization of the blood's oxygen for the oxidation of alcohol entails a corresponding loss for the tissues, the result being a reduction of the activity of all vital processes. That such is actually the case is illustrated by the fact that although Binz,[57] Jaquet[58] and Wilmanns found that respiratory activity is augmented, the quantity of carbonic dioxide eliminated is on the whole reduced, as observed by N. S. Davis, Hammond,[59] Boeck and Bauer,[60] Rumpf[61] and many other investigators. The labor of breathing is thus augmented, but intracellular metabolism is impaired, owing to the paucity of oxygen. Indeed, Bouchardat and Sandras[62] observed in a rooster intoxicated with alcohol that the comb became cyanotic. This is apparently contradicted by the observations of Demarquay, Duméril, Perrin and others that small doses either do not modify the temperature, or, as noted by Wood,[63] raise it slightly, *i.e.*, about 1° F. (0.4° C.). All these and many other investigators have found, larger doses, *i.e.*, doses capable in this connection of seriously deoxidizing the blood, lower the temperature in proportion as the quantity is large.

The more recent observations tend, however, to disprove much of the older work. Sollmann for instance concludes as a result of his studies including a comprehensive review of the literature of alcohol "that there is an increase in the rate of the respiration and of the heart, the blood-pressure rises." He states, moreover, "that 'stimulant' doses of alcohol increase the depth of the respirations quite markedly and that the amount of respired air may be doubled." This coincides with

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[51] Schulinus: Archiv. f. Heilkunde, Bd. vii, S. 97, 1866.
[52] Buchheim, Nothnagel and Rossbach: "Therap.," p. 350, 1880.
[53] Lieben: Ann. d. Chem. u. Pharm., Bd. vii Supp., S. 236, 1870.
[54] Atwater and Benedict: S. E. Dept. of Agricul. Exp. Station Bull. No. 69.
[55] Abelous, Bardier and Ribaut: C. r. de la Soc. de biol., vol. lv, p. 420, 1903.
[56] Cushny: *Loc. cit.*, p. 139, fourth edition, 1906.
[57] Binz: Centralbl. f. klin. Med., S. 407, 1895.
[58] Jaquet: Archives de pharmacodynamie, vol. ii, 1895.
[59] Hammond: Physiol. Memoirs, p. 43, Phila., 1863.
[60] Boeck and Bauer: Zeit. f. Biol., Bd. x, S. 336, 1874.
[61] Rumpf: Arch. f. d. ges. Physiol., Bd. xxxiii, S. 538, 1884.,
[62] Bouchardat and Sandras: Manquat: *Loc. cit.*, vol. ii, p. 657.
[63] Wood: *Loc. cit.*, p. 294, thirteenth edition, 1906.

the increased functional activity, caused by moderate doses of alcohol, of the adrenal and thyroid previously mentioned.

Alcohol is not a food; it does not replace proteids, fats or carbohydrates. The heat energy it liberates when oxidized first accelerates metabolism then slows it if the dose ingested is large. The tissues being deprived of the oxygen thus consumed by alcohol, catabolism is correspondingly delayed; and this in turn, proportionally retards the assimilation of materials by the tissues. The only effect of alcohol absorbed from the alimentary canal, therefore, especially in view of the fact that it supplies the organism with no tissue-building material, is to interfere with the nutritional process. In other words, it only spares the proteids, fats and carbohydrates as do asphyxiating agents, *i.e.*, by hindering tissue respiration.*

Alcohol is believed by some investigators to replace proteids, and by the majority of them to replace fats and carbohydrates. H. F. Hewes[98] aptly remarks in this connection: "The property of sparing tissue is possessed by several narcotic substances, as morphia. It would be as reasonable to class this substance among the foods as alcohol, if this property were taken as the distinctive quality of a food." Indeed, the greatest authority on thermochemistry, the late Prof. Berthelot,[99] held that alcohol is not a food.

Atwater and Benedict, in the exhaustive study referred to, conclude that the potential energy of alcohol is converted in the organism into working energy as thoroughly as is that of ordinary food. This cannot be accepted in the sense that alcohol can replace food, since the energy liberated is merely heat energy. As emphasized by F. S. Benedict,[100] alcohol does not build muscular or adipose tissue, thus failing in the essential rôle of true foods; it only furnishes a supply of heat while being oxidized. Indeed, were the working energy thus liberated, alcohol would exceed considerably in value that of ordinary ailments, since, as calculated by Dupré,[101] alcohol liberates during its oxidation nearly five times the heat units that an equal quantity of lean beef would produce. Kassowitz[102] has likewise laid stress on the fact that alcohol only acts as a stimulus, and that the substitution of a given proportion of non-nitrogenous food by a quantity of alcohol of equal caloric value, is associated with diminished working capacity and a dissipation of vital resources.

All this is further emphasized by the fact that concurrently with increased heat production, alcohol causes decreased nitrogen excretion. Thus, Bevan Lewis[103] ascertained calorimetrically that, while, as a rule, the heat production was at first lessened in rabbits by small doses, this was replaced by a considerable increase in heat production, especially after large doses. This was confirmed by E. T. Reichert and H. C. Wood[104] in dogs. The greater relative heat-value of large doses is obvious in these experiments, and yet, Norris and Smith[105] found that 1.9 c.c. to the kilo of animal increased the excretion of nitrogen two per cent., but that 2.3 c.c. per kilo *decreased* it two per cent. This reached nearly nine per cent. when 2.7 c.c. per kilo were used.

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* *Author's conclusion.*

[98] H. F. Hewes: Boston Med. and Surg. Jour., Sept. 6, 1900.

[99] Berthelot: Brit. Med. Jour., Mar. 14, 1903.

[100] F. S. Benedict: Boston Med. and Surg. Jour., July 10, 1902.

[101] Dupré: Practitioner, July, 1872.

[102] Kassowitz: Pflüger's Arch. f. Physiol., Bd. xc, S. 421, 1902.

[103] Bevan Lewis: Jour. Ment. Sci., Apr., 1880.

That the waste of heat energy simply inhibits tissue metabolism is shown by the diminution of catabolic products. Hammond[106] found that alcohol decreased the excretion of urea, chlorine and phosphoric acid. Riess[107] observed that it lessened the excretion of chlorides, phosphates and sulphates, and to a marked degree that of urea. Rosenfeld[108] and other investigators, after producing nitrogenous equilibrium in man, found the nitrogen elimination distinctly decreased, *i.e.*, lower than the intake. Alcohol was undoubtedly the active factor in this morbid process, for while A. Ott[109] observed an extremely low excretion of nitrogen the first day alcohol was used, H. Keller,[110] on the other hand, found that as soon as the use of alcohol ceased, the excretion of nitrogen rose rapidly until it was one gm. above normal—this excess persisting three days. Indeed, Miura[111] was led to conclude, by a series of comprehensive experiments also showing a marked decrease of nitrogen, that the effects of alcohol in this particular were similar to those of a reduced diet.

This is equally true of carbohydrates. Miura found that when sugar was replaced by isodynamic quantities of alcohol, a low nitrogen excretion occurred in subjects placed in a condition of nitrogenous equilibrium, but that on restoring the sugar the nitrogenous equilibrium was resumed. It is evident, therefore, that alcohol is not a substitute for carbohydrates. This accounts for the fact recorded by explorers in the Arctic regions, that the use of alcohol greatly reduced their resistance to cold. Again, Chittenden[112] found that alcohol reduced oxidation in the liver. This he characterises a pernicious influence of which carbohydrates and fats are free. While the latter bodies are simply oxidised into carbonic acid and water and converted into glycogen and fat, alcohol is not. He concludes, therefore, that this establishes a distinct line of demarcation between alcohol on the one hand and carbohydrates and fats on the other. And this applies to the rest of the organism as well. Briefly, in the words of Woodbury and Egbert,[113] the physiological action of alcohol on the human body is destructive, but never constructive.

Untoward Effects.—The first stage of alcohol poisoning, that known as drunkenness, may be provoked by varying doses, small quantities sufficing, in persons unaccustomed to its use, to produce phenomena which only occur after the ingestion of large quantities in habitual drinkers.

When a so-called "stimulating" dose of alcohol is ingested, it liberates heat-energy while being oxidized by the adrenoxidase in the blood, and the quantity of energy thus liberated is in excess of that produced normally by the interaction of the adrenoxidase and nucleo-proteid.* An artificial exacerbation of metabolism being thus provoked in all tissues, the contractile power of the cardiac and vascular muscles is correspondingly increased.* As a result, the heart-beats and pulse become stronger and more frequent, and the blood-pressure is raised, the blood being projected forcibly into all capillaries. The latter being passively dilated and congested, the well-known flushed face and eye, the warm skin, the strong and rapid pulse, the cerebral excitement which prompts to garrulousness, boisterousness, outbursts of anger, etc., and the temporary augmentation of physical strength, are produced.

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[104] E. T. Reichert and H. C. Wood: Cited by Wood: *Loc. cit.*, p. 295, thirteenth edition, 1906.

[105] Norris and Smith: Jour. of Physiol., vol. xii, p. 220, 1891.

[106] Hammond: *Loc. cit.*

[107] Riess: Zeit. f. klin. Med., Bd. ii, S. 1, 1881.

[108] Rosenfeld: Die Therapie der Gegenwart, Bd. vii, 1900.

[109] A. Ott: Arch. f. exp. Path. u. Pharm., Bd. xlvii, S. 267, 1902.

[110] H. Keller: Zeit. f. physiol. Chemie, Bd. xiii, S. 128, 1889.

[111] Miura: Zeit. f. klin. Med., Bd. xx, S. 137, 1892.

[112] Chittenden: Med. News, Apr. 22, 1905.

[113] Woodbury and Egbert: Jour. Amer. Med. Assoc., Mar. 31, 1900.

When a depressing dose is taken, this stage is soon antagonized in two ways: (1) The alcohol and adrenoxidase being free in the blood, while nucleo-proteid is secreted in the latter by leucocytes only as needed,* the reducing action of the alcohol deprives the adrenoxidase of oxygen which it should supply to the tissues.* Metabolism being impaired in proportion, and the nerve centers, general and subsidiary (including the vasomotor centers), and the muscularis of all vessels receiving partially reduced blood,* general vasodilation (including relaxation of the cutaneous arterioles) follows, and the capillaries of all organs, including the skin and brain, are the seat of a passive hyperæmia. The pulse is still full at this stage, but easily compressed.

The exacerbation of muscular power coincides, as is well known, with the period of cerebral excitement and with the characteristic congestion of the face, eyes, etc. Cushny[114] writes: "The flushing of the skin, which occurs in alcoholic intoxication, would seem to point to some vascular action, but it is impossible to say at present what the nature of this action is. It indicates dilation of the skin vessels, but whether this is of central or peripheral origin, whether due to stimulation or dilator centers or paresis of vasoconstrictors, it is impossible to say." As Claude Bernard pointed out that marked hyperæmia of the brain was also present, the cause of this phenomenon may be said to be as obscure as that of the facial hyperæmia; and this applies as well to the muscular erethism.

Castillo,[115] Binz,[116] Eagleton,[117] Kochmann[118] and others have witnessed the preliminary rise of the blood-pressure referred to. Abel,[149] Rosenfeld,[150] Cabot[151] and others did not observe it; while the third phase, vasodilation, was noted by Zimmerberg,[152] Gutnikow,[153] Pässler,[154] Schule[155] and Rosenfeld. The fact that all three phases may occur, as shown above, accounts for the contradictory results recorded by various investigators.

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* *Author's conclusion.*

[114] Cushny: *Loc. cit.*, p. 137, fourth edition, 1906.

[115] Castillo: Phila. Med. Times, Oct. 23, 1890.

[116] Binz: *Loc. cit.*

[117] Eagleton: Univ. Med. Mag., Sept., 1890.

[118] Kochmann: Deut. med. Woch., Bd. xxxi, S. 942, 1905.

That the vasoconstriction is due to augmentation of the metabolic processes in the vascular walls by the direct action of the alcoholised blood is also indicated by the fact that these investigators, Wood and Hoyt,[156] noted that alcohol "elevates the blood-pressure after vasomotor paralysis from section of the cervical cord." Their experiments tended to show, moreover, that the cerebral excitement and increased activity were due "to the enormously increased flow of blood running riot through the cerebrum." Hemmeter[157] likewise observed a marked increase in the rapidity of the blood-flow, and a still greater one when more alcohol was administered; in some of Wood and Hoyt's experiments the speed of the current increased 33 per cent. The red face and the still redder nose and eyes of the common drunkard attest to the fact that after the prolonged use of alcohol the arterioles may remain dilated. Finkelnburg[158] found, by introducing a trocar between the vertebræ, that the cerebro-spinal pressure was considerably increased.

As to the influence of the general vasoconstriction upon the capillaries, Kochmann[159] found experimentally that "in moderate doses alcohol increases the vascular tension; when the rise is at its maximum, the peripheral vessels are dilated." He noted, moreover, that the latter effect was produced "even when the doses are too weak to cause an increase of vascular tension."

The influence of large doses is shown by the experimental observation of Wood and Hoyt[160] that "sometimes no effect was produced until the alcohol had been given in sufficient amounts to reduce the pressure." Vasodilation may also occur under the influence of small doses. Thus, Kellogg[161] states that "the full bounding pulse usually produced by the administration of an ounce or two of brandy properly diluted, gives the impression of an increased vigor of heart action, but it is only necessary to determine the blood-pressure by means of a Riva-Rocci instrument, or Gaertner's tonometer, to discover that the blood-pressure is lowered instead of raised. This lowering may amount to twenty or thirty millimeters, or even more."

While the varying effects produced by alcohol indicate that it has no direct action on the vasomotor center (which would always be influenced in the same way) they suggest, on the other hand, that it is due to an intravascular chemical process. Cabot[162] found that alcohol did not influence the temperature in febrile cases, as shown by 1105 measurements taken by him before, during and after its administration—an observation confirmed in animals by Wood and Hoyt. This

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[149] Abel: "Physiol. Aspect of the Liquor Problem," vol. ii, 1903.

[150] Rosenfeld: *Loc. cit.*

[151] Cabot: Trans. Assoc. of Amer. Phys., vol. xviii, p. 462, 1903.

[152] Zimmerberg: Dissert. Dorpat, 1869, cited by Cabot: *Loc. cit.*

[153] Gutnikow: Zeit. f. klin. Med., Bd. xxi, S. 152, 1892.

[154] Pässler: Verh. Congr. f. inn. Med., Bd. xvi, S. 436, 1898.

[155] Schule: Berl. klin. Woch., Aug. 13, 1900.

[156] Wood and Hoyt: Memoirs of the National Acad. of Sciences, vol. x, Third Mem., 1905.

[157] Hemmeter: Med. Rec., Sept. 12, 1891.

[158] Finkelnburg: Deut. Arch. f. klin. Med., Bd. lxxx, S. 130, 1904.

[159] Kochmann: Arch. inter. de pharmacodyn. et de thérap., T. xv, p. 443, 1905.

[160] Wood and Hoyt: Univ. of Penna. Med. Bull., May, 1905.

[161] Kellogg: Modern Medicine, Nov., 1906.

[162] Cabot: *Loc. cit.*

FIBROSIS OF ANTERIOR PITUITARY DUE TO ALCOHOLISM. *[Magnus.]*

is readily explained by the affinity of alcohol for oxygen. Fever being accompanied by a marked increase in the blood's oxygen ratio, the alcohol can be oxidised at the expense of the surplus of this gas and be itself consumed in the febrile process without appreciably modifying existing conditions. In the healthy individual, however, the conditions are reversed; there is no excess of oxygen in the blood, and the latter's oxygen being in part consumed by the alcohol, functional disturbances occur, *i.e.*, inadequate tissue metabolism, as shown by the reduced excretion of CO_2 and nitrogen, lowered heat-production and temperature and other morbid phenomena reviewed. As it is *only* in healthy individuals, therefore, that the variations of blood-pressure have been observed, and since these cannot be ascribed to a direct action of the alcohol upon the vasomotor center, they must be ascribed to a chemical process in the blood itself, *i.e.*, in the vessels.

This is further shown by the fact that alcohol so modifies the blood's physical properties that its access to the tissues is hampered. Thus, Bouchard[133] states that alcohol, owing to its feeble osmotic power, inhibits nutrition by delaying the penetration of plasma into the cellular elements. Burton-Opitz[134] found that it reduced the alkalinity of the blood, and rendered the latter abnormally viscid. Even the adrenoxidase, a globulin, must lose some of the fluidity so essential to its circulation in the cellular elements, since, as stated by Halliburton,[135] "it can be shown that the globulins require a lower percentage of alcohol to precipitate them than the albumins."

Cellular metabolism being now inhibited to a marked degree,* the sthenic symptoms are replaced by general asthenia and maudlin hebetude: the skeletal muscles become relaxed and unable to respond adequately to nervous impulses. The gait becomes staggering, the movements irregular and uncertain, the speech thick and difficult, and the eyes half closed owing to relaxation of the palpebral muscles.

Alcohol being converted by oxidation into water and carbonic acid and the excretion of the latter being interfered with through the increased viscosity of the plasma, an asphyxia-like condition, sometimes attended with beginning cyanosis, is initiated. This finally causes the patient to fall into a deep torpid slumber accompanied by stertorous breathing, due to relaxation of the palatal muscles.

The blood is depleted to such a degree of its oxygen in the larger vessels that it is practically venous on reaching the minute intercellular capillaries. The experiments of Warren P. Lombard,[136] Dastre,[137] Horsley,[138] Destrée,[139] Scheffer[140] and others have shown that alcohol caused, at first, an exacerbation of strength, which was soon replaced by marked weakness if the dose was sufficient, and that large doses invariably reduced the muscular power. That the adynamia is not due to the direct action of the alcohol on the muscle fiber is shown by the statement of Cushny's[141] that "alcohol has no effect on muscle or on peripheral nerves when it is carried to them by the blood." The period of increased muscular power is due, we have seen, to passive hyperæmia of the muscular elements, a fact which indicates that it is fictitious. Indeed, as shown by Destrée and others, fatigue soon sets in and becomes marked. This accounts for the fact that troops deprived of alcohol stand long marches with much less fatigue than those supplied with it. This was emphasized anew recently by Beyer[142] and Fritig. The latter observer states that since Dutch officers and men were given, in 1898, the option of drawing the money value of their alcoholic ration, the many who ceased to use alcohol have shown a noticeable increase in their resistance to fatigue and disease. Conversely, those who consumed alcohol, while competent for duty during peace, quickly succumbed to these conditions during active service. Alcohol thus debilitates the muscular system even when not taken in toxic doses. Abel[143] states that "we have no experimental grounds for believing that small or even moderate quantities of alcohol exercise any beneficial direct action on the muscles of man and warm-blooded animals."

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* *Author's conclusion.*

[133] Bouchard: *Loc. cit.*

[134] Burton-Opitz: Jour. of Physiol., vol. xxxii, p. 8, 1904.

[135] Halliburton: "Biochemistry of Muscle and Nerve," p. 22, 1904.

[136] Warren P. Lombard: Jour. of Physiol., vol. xiii, p. 1, 1892.

[137] Dastre: C. r. de la Soc. de biol., vol. ii, p. 796, 1896.

[138] Horsley: Lancet, May 5, 1900.

[139] Destrée: Quart. Jour. of Inebriety, Jan., 1900.

[140] Scheffer: Arch. f. exp. Path. u. Pharm., Bd. xliv, S. 24, 1900.

The third stage includes the symptoms witnessed in individuals said to be "dead drunk." Here an entirely different order of phenomena is observed. The patient is unconscious, pale or perhaps cyanotic, and his surface is insensible and cold. All the senses are in abeyance. The pulse is thin and compressible and the temperature sometimes extremely low. This condition may continue several hours—cases in which it lasts over twelve hours being usually fatal—and gradual recovery occur, or the respiration may become distant, feeble and shallow, and death ensue from arrest of this function.

This is due not only to the physical alterations and viscidity of the blood, but also to its accumulation in the large central trunks, especially those of the splanchnic area. The peripheral organs, including the brain, being partially depleted, their functions are almost in abeyance. When this reaches a certain limit the two lobes of the pituitary are themselves rendered sufficiently ischæmic to paralyze their functions, and death ensues.

A small quantity of alcohol added to sea-water containing very young fertilized sea-urchin eggs delays markedly cell-division and gastrulation, and so impedes the motility of the mesenchyma cells that the development of the skeleton is markedly impaired. This is due to the deprivation of what oxygen the alcohol consumes, metabolism in the cellular elements being correspondingly slowed. The action of alcohol on the human tissue-cell differs in no way from that on the eggs of the sea-urchin. Possessed of a marked affinity for water, it is rapidly distributed throughout the blood-stream and at once enters upon its deadly work; the degree of harm done being commensurate with the quantity thus disseminated.

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[141] Cushny: *Loc. cit.*, p. 139, third edition, 1899.
[142] Beyer: Boston Med. and Surg. Jour., Aug. 22, 1901.
[143] Abel: *Loc. cit.*

Another feature of the morbid process forcibly asserts itself at this stage of poisoning. As is well known and as recently emphasized by Hodge,[144] traces of alcohol suffice to inhibit the growth of yeast. Dastre,[145] on the other hand, found that while soluble ferments could exercise their specific action in relatively strong solutions of alcohol—15 to 20 per cent. in the case of trypsin—the blood's soluble ferments, including fibrin ferment, are but slightly soluble even in very weak solutions of alcohol, *i.e.*, 4 per cent. The fibrin ferment being, as I have shown, the *adrenoxidase*, it follows that the large quantity of alcohol ingested in the production of the third stage not only dispossesses this substance of the oxygen it should carry to the tissues, but that it actually paralyzes it.

It is when bereft of its vitalizing properties, therefore, that the blood reaches the nerve-centers. Indeed, that alcohol is a paralysant of the nervous system has been strongly urged by Bunge,[146] Schmiedeberg,[147] Ach and Kraepelin,[148] Crothers[149] and many other investigators, while Dogiel found that large doses depressed markedly not only the motor, but also the sensory nerve-centers. This necessarily applies to the most sensitive of them all, those of the pituitary body. The very source of the body's *pabulum vitæ* is thus rendered sterile, since the adrenals must soon cease to functionate as well as their center.

The *treatment of alcohol poisoning* is described in a special section at the end of this volume.

Therapeutics.—The present conception of the therapeutic value of ethyl alcohol in disease is based on a misinterpretation of the rôle of the kinetic energy yielded while this agent is being burnt in the body.* The claim that it is an albumin-saving food, the value of which corresponds with its dynamic equivalent of pure food hydrocarbon, falls, when the process through which it saves albumin is taken into consideration. To rob the blood of its oxygen is an albumin-saving process, but at the expense of cellular life;* to increase the viscidity and decrease the alkalinity of the blood is an albumin-saving process, but by inhibiting life.* On the other hand the kinetic energy it liberates in the form of heat contributes nothing to the vital process.* Alcohol, therefore, is valueless as a food.

Evidence to this effect has already been submitted. This view is further emphasized from another standpoint by Winfield S. Hall[150] in the following words: "Ethyl alcohol possesses several characteristics in common with the carbonaceous foods, *e.g.* (1) it is composed of C, H and O; (2) it is readily oxidized in the liver, yielding CO_2 and H_2O, which are excreted; (3) it yields heat incident to its oxidation, and this heat naturally augments the body income of heat; (4) ingestion of ethyl alcohol leads to a decrease in the catabolism of carbonaceous foods, and may even 'spare' proteins.

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* *Author's conclusion.*

[144] Hodge: "Physiol. Aspects of the Liquor Problem," June, 1903.

[145] Dastre: Arch. de Physiol., T. viii, p. 120, 1896.

[146] Bunge: "Die Alkoholfrage," Leipzig, 1886.

[147] Schmiedeberg: "Grundriss der Arzneimittellehre," Leipzig, 1895.

[148] Kraepelin: Münch. med. Woch., Bd. xlvi, S. 1365, 1899.

[149] Crothers: Jour. Amer. Med. Assoc., Dec. 5, 1903.

[150] Winfield S. Hall: *Ibid.*, Feb. 2, 1907.

"In this connection, one must not lose sight of the following facts: (1) All vegetable toxins and alkaloids are composed of the same kind of chemical elements as enter into foodstuffs, viz., C, H, O and N. (2) Toxins and alkaloidal poisons in general are oxidized in the liver through the agency of oxidases, whose function is to oxidize, and thus to make harmless, substances which would act as protoplasmic poisons on all cells with which they come in contact. When moderate amounts of such toxins are taken the defences of the system are sufficient to reduce them to a harmless condition and no immediate injury results. If larger quantities are ingested the full drug effect (narcotic in the case of alcohol) is immediately experienced, the oxidases of the system being unable to defend it against a large dose. (3) All oxidation yields heat, whether it is a normal catabolism or a protective oxidation. That the heat from the oxidation of alcohol is not a normal catabolism for the purpose of heat liberation is evident from the fact that, notwithstanding the liberation of heat through oxidation of alcohol, the temperature of the body falls, because of increased loss of heat from the surface. This increased loss is due to dilatation of peripheral vessels. (4) Decreased catabolism of carbonaceous or nitrogenous foods following ingestion of a narcotic is a universal fact depending on the drug effect and giving to the oxidized narcotic no significance as a food. It may be said without reservation that ethyl alcohol is not a food in the scientific significance of the word."

In small doses, alcohol, by supplementing the heat energy normally produced (through the interaction of adrenoxidase and nucleo-proteid*) with the artificial energy liberated while it is being oxidized, augments momentarily the activity of metabolism* and the antitoxic activity of the blood. Its action, in this connection, becomes serviceable when, after exposure to cold and damp, the accumulation of toxic wastes under the skin (through the depressing effect of cold upon cutaneous metabolism*) and other conditions which render the body vulnerable to disease, a prophylactic is demanded; or to counteract promptly (especially if given in warm water) the toxic effects of *depressing poisons*, such as *ptomains, vemons, chloral, veratrum viride, mushroom poisoning, etc.*

As to the use of alcohol in febrile diseases, however, its physiological action is such as to interfere with the blood's defensive processes.* The belief of its advocates that it does good by lowering the temperature, the blood-pressure and the pulse-rate, is based on the view that fever is a pathological phenomenon. In truth, fever is the expression of the body's power to defend itself; and if enough alcohol is given to lower the temperature, it can serve only to disarm Nature's own weapons.*

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* *Author's conclusion.*

G. Rubin[151] found experimentally that alcohol decreased decidedly the resistance of animals to infection. No organic lesions were present, and it appeared to weaken directly the substance or substances that inhibited the growth and toxic action of bacteria, and which seemed to be derived from the leucocytes. These cells themselves appeared to be morbidly influenced. The two phases of the action of alcohol on the immunizing process—the primary ephemeral spurt of antitoxic activity, and the secondary and marked depressing influence—are well exemplified in the following quotation from H. C. Wood's treatise:[152] "Binz[153] found that alcohol increases the resistive power of the dog to septic material, but his experiments seem to have been too few to be of value. In an incomplete research, H. A. Hare and M. E. Pennington[154] found that alcohol increases the bactericidal property of the blood at least against some pathogenic organisms. Gruber[155] affirms, as the result of experimentation, that the frequent administration of small doses of alcohol to guinea pigs, injected with bacillus prodigiosus, prolonged life, and in some instances even brought about restoration. Opposed to these results are those of various investigators. Doyen[156] and Thomas[157] both found that alcohol increases the liability of animals to infection with cholera. Abbott,[158] using streptococcus pyogenes, bacillus coli, or staphylococcus pyogenes aureus, found that the alcoholized animals died with much more certainty than did those of the control experiments, in which no alcohol was given. Deléarde[159] reached the result that alcohol destroys the immunization of rabbits against tetanus and anthrax. Laitinen,[160] in a very elaborate research upon three hundred and forty-two animals, representing six species of mammals and birds, using anthrax, tubercle bacilli, and diphtheria toxin, arrived at the conclusion that alcohol diminishes very distinctly the resistance of the body towards infections. Pawlowsky[161] found that alcoholized animals reacted much more freely to staphylococcus citreus than did the normal animal. Kögler and Gruber[162] determined that alcoholization increases the mortality of animals infected with the pneumobacillus. Goldberg[163] came to a similar conclusion in regard to the influence of anthrax on pigeons. Ausems[164] found that the administration of alcohol in small doses to rabbits before infection diminished their resistance." Although the results of both sets of observers harmonize with my views, the fact remains that those who found that alcohol inhibited the protective functions are decidedly in the majority.

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* *Author's conclusion.*

[151] G. Rubin: Jour. Infect. Dis., May 30, 1904.

[152] H. C. Wood: *Loc. cit.*, p. 305, thirteenth edition, 1906.

[153] Binz: Verh. Congr. f. inn. Med., Bd. vii, S. 70, 1888.

[154] H. A. Hare and M. E. Pennington: Therap. Gaz., May 15, 1903.

[155] Gruber: Wiener klin. Woch., Bd. xiv, S. 479, 1901.

[156] Doyen: Arch. de physiol., 3 série, T. vi, p. 179, 1885.

[157] Thomas: Arch. f. exp. Path., Bd. xxxii, S. 38, 1893.

[158] Abbott: Jour. of Exper. Med., vol. i, p. 447, 1896.

[159] Deléarde: Arch. inter. pharmacodyn., vol. iv, 1897.

[160] Laitinen: Zeit. f. Hygiene u. Infekts., Bd. xxxiv, S. 206, 1900.

[161] Pawlowsky: *Ibid.*, Bd. xxxiii, S. 261, 1900.

[162] Gruber: Wiener klin. Woch., Bd. xiv, S. 479, 1901.

[163] Goldberg: Centralbl. f. Bakter., Bd. xxx, S. 696, 731, 1901.

[164] Ausems: Diss. Utrecht, 1900; Centralbl. f. inn. Med., Bd. xxiii, S. 536, 1902.

BROMIDES.

(Bromides of Potassium, Sodium, Lithium, etc.)

Physiological Action.—The primary effect of potassium bromide is to depress the functional activity of the general vasomotor center and thus to cause relaxation of all vessels provided with a muscular coat.* The large central vascular trunks accommodating more blood, the capillaries of all organs, particularly those of brain and skin, are more or less depleted and their functional activity is correspondingly lowered.* Hence its quieting influence on cerebral excitement and its anæsthetizing effect upon the cutaneous sensory and end-organs, the main feature of its action as depresso-motor agent.*

The ephemeral tetanoid condition observed in frogs by Laborde,[165] Purser[166] and others, when even small doses are injected, is but a proof of the relaxation of the arteries. The peripheral arterioles being also relaxed, an influx of blood in the capillaries of the skin takes place and the sensory end-organs being suddenly stimulated, they incite reflex spasm. But this stage is temporary. As is well known, the spasms caused by strychnine in frogs can be prevented by anæsthetizing the skin. The depletion caused by the bromides produces a similat anæsthesia. During poisoning, this may become so marked that, as observed by Purser in frogs and Eulenberg and Guttmann[167] in rabbits, the animal, though able to jump, may be pricked, pinched or burned, and yet show no evidence of pain. The supply of blood to the peripheral capillaries is soon reduced and the true effects of the drug appear. "After a short time," writes Wood,[168] "this stage of muscular excitement gives way to one of great muscular relaxation and total abolition of reflex actions"—the capillaries of the contractile elements being themselves deprived more or less of blood.

The action on the brain is similar. The congestive stage due to relaxation of the terminal arteries is occasionally witnessed, the drug then causing headache, irritability and redness of tongue (Manquat), or what has been termed "bromomania," cases of which have been reported by Voisin, Stark, Kiernan, Moyer, Rockwell, Spitzka and others.[169] As a rule, however, the recession of blood occurs before excitation can take place. As shown by Albertoni[170] it so obtunds the sensitiveness of the cortex that its electrical excitation can no longer provoke epileptiform convulsions, while Sokolowsky[171] observed that "large doses of bromide cause *anæmia* of the brain." That this is due to recession of the blood, due, in turn, to general vasodilation, is shown by the fact that Schouten[172] found manometrically that even small doses of potassium bromide lowered the blood-pressure. De Fleury has also observed this phenomenon. A similar effect is caused, as is well known, by dividing the upper part of the spinal cord, *i.e.*, the general vasomotor path, and by removal of the pituitary body, the seat of the general vasomotor center.

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* *Author's conclusion.*

[165] Laborde: Arch. de physiol., T. i, p. 422, 1868.

[166] Purser: Dublin Jour. Med. Sci., vol. xlvii, p. 321, 1869.

[167] Eulenberg and Guttmann: Virchow's Archiv, Bd. xii, S. 91, 1867.

[168] Wood: *Loc. cit.*, p. 240, thirteenth edition, 1906.

[169] Cited by Stockwell: Sajous's "Cyclo. of Pract. Med.," vol. ii, p. 7, 1898.

[170] Albertoni: Arch. f. exp. Path. u. Pharm., Bd. xv, S. 256, 1882.

[171] Sokolowsky: Manquat: *Loc. cit.*, vol. ii, p. 739.

[172] Schouten: Arch. f. Heilkunde, Bd. xii, S. 97, 1871.

The diminution of blood in the capillaries of the various organs[*] impairs their functional activity. The temperature is lowered and the sensibility of the mucous membranes and the skin is more or less reduced. Mental torpor, defective memory, difficult enunciation, somnolence, depression of spirits (lapsing at times into melancholia) are also observed in some cases when the doses are frequently repeated. Digestion is impaired in some subjects, owing to deficient secretion of saliva and gastric juice. Sexual weakness is often produced, erethism of the sexual organs necessitating a marked degree of vascular engorgement. A similar deficiency of blood in the arterioles of the iris[*] may also cause dilation of the pupils. The circulatory torpor[*] in the skeletal muscles may entail muscular relaxation and weakness; but of all the muscular organs, the heart suffers most from the deficiency of blood,[*] and its contractile power is greatly diminished. This constitutes an additional factor in the morbid process, since it tends further to reduce both the vascular pressure and the speed of the blood-current in the capillary system.

As shown below, the temperature of the surface is reduced by bromides—a phenomenon partly due to the recession of blood to the deeper vessels. Quite familiar to all laryngologists is the diminution of sensibility of the mucous membrane of the pharynx and larynx, which is quite perceptible after a single dose of 30 grains (2 gms.). The cerebral phenomena are also of common observation. Gubler[174] found that 2 to 4 gms. (30 to 60 grains) daily sufficed in some cases to induce melancholia, even in maniacal subjects. Weir Mitchell[175] and others have reported similar instances. Diminution of the salivary secretion was observed by Gubler, Rabuteau[176] and other clinicians. As to the influence of vascular depletion on the pupil, Landois[177] states, referring to the blood-vessels of the iris, that "everything that diminishes the amount of blood dilates the pupil." As to the rôle of the heart in the morbid process Wood[178] concludes that "the fall of the arterial pressure is certainly largely of cardiac origin," though he considers it probable that "the vasomotor system also shares the paralyzing influence of the drug."

Bromism.—When large doses are administered during a prolonged period, the oxygenizing power of the blood becomes inadequate.[*] This is due to the fact that, as is the case with all organs that are remote from the splanchnic area (in which the blood accumulates when the vessels are dilated), the pituitary body also becomes ischæmic, and the adrenals are inadequately stimulated.[*] Their secretion being materially reduced, the proportion of adrenoxidase formed is insufficient to satisfy the needs of the organism at large, *i.e.*, to sustain nutrition.[*]

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[*] *Author's conclusion.*

[174] Gubler: Manquat: *Loc. cit.*, vol. ii, p. 738.

[175] Weir Mitchell: Trans. Assoc. of Amer. Phys., vol. xi, p. 196, 1896.

[176] Rabuteau: Gaz. hebdom., 2 série, vol. vi, p. 177, 1869.

[177] Landois: "Physiology," tenth edition, p. 842, 1905.

[178] Wood: *Loc. cit.*, p. 344, thirteenth edition, 1906.

The condition known as "bromism" appears when this condition is added to the primary vasomotor paresis caused by the drug.[*] It is mainly due to the fact that, owing to the impaired catabolism and to the resulting torpor of the eliminatory functions of the skin, kidneys, intestinal and respiratory tracts, the drug and imperfectly catabolized wastes accumulate in the system at large. Hence the marked cutaneous disorders observed in this condition, the latter varying from an erythematous and rubeoliform blush to acne, pustules, furuncular swellings, more or less extensive ulcerations and even gangrene—all aggravated by the cutaneous denutrition. A typical sign of adrenal insufficiency[*] is frequently observed in these cases, viz., copper-colored blotches.

The other symptoms of bromism are but exaggerations of those produced by smaller quantities of the drug.[*] Mental torpor lapses into stupidity, the facial expression recalling that of an idiot. The senses are also greatly weakened. The eyes lose their lustre, and are surrounded by dark rings, and the pupils are more or less widely dilated. Hallucinations, visions, utter listlessness or melancholia with outbursts of mania, may precede the ultimate issue, cerebral paralysis. The muscular weakness gradually becomes complete adynamia. The temperature is greatly reduced, the heart's action is hardly perceptible and the respiration becomes correspondingly feeble and shallow. The patient gradually sinks into a condition of general impotence, hardly able even to ingest his food, liable at any moment to be carried off by some intercurrent disease, especially pneumonia, or to lapse suddenly into coma, the precursor of death.

The action on the adrenal center is but a counterpart of that on other organs. The inhibition of the functions of the salivary glands observed by Gubler, Rabuteau and others, illustrates the action of the drug on secretory organs in general. The diminution of saliva merely typifies, therefore, the corresponding effect on the adrenals, *i.e.*, a diminution of secretion. The deficiency of adrenoxidase in the blood normally causes a reduction of the temperature. Martin-Damourette and Pelvet[179] found that the entire surface was hypothermic. Wood[180] also states that in warm-blooded animals, toxic doses of potassium bromide lower very decidedly the temperature. This is, in part, due to the recession of blood from the surface; but actual reduction of activity of all oxidation processes is shown by the fact observed by H. Bill,[181] that the elimination of carbon dioxide from the lungs is markedly decreased by large doses. The excretion of urea has been studied by various investigators, but with contradictory results—a fact explained by the renal irritation, which, according to Pletzer,[182] large doses provoke. Skoog,[183] who reported several cases of bromism, including some presenting mental disturbances, noted that "after a few weeks cellular resistance is lowered, the degree depending on the individual susceptibility and amount of drugging."

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[*] *Author's conclusion.*

The torpor of the blood-stream in the capillaries, coupled with the lowered oxidizing efficiency of the blood itself, favors the accumulation of the drug in the system. Wood states that it is undoubtedly to be found in every tissue of the body, and refers to the labors of Doyon and Cazeneuve,[184] confirmed by those of Féré and Herbert,[185] as showing that bromide of potassium "is stored up in the nerve-centers much more largely than elsewhere." The elimination occurs, in part, through the skin as shown by eruptions, pustules having been found by Guttmann[186] and others to contain the drug. The violet areola observed around the cutaneous lesions is characteristic of bromism, according to Féré.[187] It is doubtless partly due to the deficient local oxygenation, and the precursor of the gangrenous plaques observed by Malherbe,[188] Darnall[189] and others. That the salt is also eliminated in the perspiration, the urine, and the fæces is well known.

The predilection of cases of bromism to pneumonia has been emphasized by Féré. Baker[190] ascribes the predisposition of epileptics to phthisis to the excessive use of bromides. Cushny[191] states that the patient "is, of course, liable to fall a victim to infectious disease," and that "in a number of cases of chronic bromide poisoning, the immediate cause of death has been an attack of bronchitis or pneumonia."

Acute Poisoning.—Acute intoxication in abnormal subjects who had not previously taken the drug is seldom, if ever, witnessed. An ounce (30 grammes) has been ingested without causing more than a temporary attack of bromism. A sensation of heat in the mouth, œsophagus and stomach, fœtid breath, intense headache (due to hyperæmia of the cerebral capillaries owing to relaxation of their arterioles*) difficult ideation and perhaps aphasia, hypothermia, cutaneous anæsthesia, weakness and irregularity of the pulse with concomitant or subsequent drowsiness which may persist several days, and be followed by slow recovery.

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[179] Martin-Damourette and Pelvet: Bull. gén. therap., med. et chir., vol. lxxiii, p. 241, 1867.
[180] Wood: *Loc. cit.*, p. 744, thirteenth edition, 1906.
[181] H. Bill: Amer. Jour. Med. Sci., July, 1868.
[182] Pletzer: Manquat: *Loc. cit.*, p. 741.
[183] Skoog: Jour. Amer. Med. Assoc., Dec. 1, 1906.
[184] Doyon and Cazeneuve: Lyon méd., vol. lx, p. 479, 1889.
[185] Féré and Herbert: C. r. de la Soc. de biol., 9 série, vol. iii, pp. 670, 760, 807, 1891.
[186] Guttmann: Virchow's Archiv, Bd. lxxiv, S. 541, 1878.
[187] Féré: C. r. de la Soc. de biol., 9 série, vol. iii, pp. 670, 760, 807, 1891.
[188] Malherbe: Presse méd., vol. vi, p. 243, 1899.
[189] Darnall: Med. Record, Sept. 7, 1901.
[190] Baker: Med. Register, Dec. 8, 1888.
[191] Cushny: *Loc. cit.*, p. 501, fourth edition, 1906.

In mammals, as well as in frogs, toxic doses cause death by provoking, as shown by Eulenburg and Guttman,[182] symptoms similar to those observed in man, *i.e.*, general paralysis of all functions. Prominent among these are the evidence of impaired oxygenation, *i.e.*, lowering of the temperature and gradual respiratory failure, the animal dying of asphyxia. The heart is invariably arrested in diastole.

The *treatment of bromide poisoning* is described in a special section at the end of this volume.

Therapeutics.—The action of the bromides thus interpreted, accounts readily for their beneficial effects in the various conditions in which they are generally employed. Though their use is to be deprecated* in *epilepsy* as curative agents, since they aggravate the disease by inhibiting catabolism and therefore the destruction of the spasmogenic wastes,* the fact that the accesses are partly due, as will be shown, to excessive vascular tension* (caused by these wastes) renders their employment permissible to ward off the attacks. This applies as well to *tetanus*, puerperal *eclampsia* and kindred disorders.* The value of the bromides in the various forms of *nervous* and *mental excitement* is likewise explained, since all nervous structures are channels for adrenoxidase.* Excitement being due to hyperæmia of nervous elements, the depletion of these elements that general vasodilation insures, affords the required relief. The same physiological process accounts* for the value of the bromides in abnormal sexual excitement, *nymphomania* for example, in *uterine disorders* due to local hyperæmia, in *seminal emissions* due to a similar condition of the spinal cord, in various subacute inflammatory disorders.

VERATRUM VIRIDE.

Physiological Action.—The action of veratrum viride has in recent years been said to resemble that of aconite, but this certainly is not the case. The symptoms ascribed by the authors of certain text-books are those of veratrine, an alkaloid derived from *Veratrum Sebadilla*, and which occurs only in traces in suitable preparations of veratrum viride and whose effects do not appear even in cases of poisoning by the latter drug. Veratrine is an unreliable agent and should not be used internally.

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* *Author's conclusion.*

[182] Eulenburg and Guttmann: *Loc. cit.*

Veratrum viride, on the other hand, is a valuable remedy when judiciously employed. By depressing directly the general* vasomotor center, it enables us to lower excessive arterial tension and to relieve an overburdened heart. It does this by causing the blood to accumulate in the splanchnic area and other great vessels of the trunk.

The most valuable observations upon the action of veratrum viride *per se* are those of H. C. Wood,[133] who found experimentally that one of the effects of the main active principle of veratrum viride, *jervine*, was a "depressing action" upon "the vasomotor centers." "The circulatory phenomena," says this author, "were primary slowing of the pulse with later rapid pulse and a progressive falling of the arterial pressure from the beginning to the end." While it is probable that the "primary slowing" was due to a slight preliminary stimulation of the general vasomotor center, the subsequent fall of blood-pressure could not be ascribed to inhibition of the heart, since Wood also says: "The slowing of the pulse was not due to any effect on the pneumogastric nerves, the jervine acting as usual after section of these nerves." The central action of the drug is emphasized by the statement that: "As, however, asphyxia, not galvanization of a sensory nerve, produces rise of pressure in the poisoned animal, it is evident that jervine depresses the vasomotor centers." Pesci[134] confirmed these observations clinically in 19 cases, all of which showed reduction of exaggerated arterial tension. Similar observations have been recorded by others.

But this applies only to experimental (and, therefore, relatively large) doses of jervine; as shown below, veratrum viride contains also a small proportion of another alkaloid, *veratroidine*, the effects of which only become manifest when large doses of veratrum viride are administered.

The vasodilation produced being commensurate with the size of the (therapeutic) dose given, we can at will regulate the vascular tension when this becomes excessive; again, as a given dose repeated at appropriate intervals sustains the effect, we can hold the blood-pressure in check until the danger is past. Finally, as the general vasomotor center recuperates promptly when the use of the drug is not too prolonged, the depression induced is readily recovered from—which is not the case when bleeding, employed with the same ends in view, is resorted to.

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* *Author's conclusion.*

[133] H. C. Wood: *Loc. cit.*, p. 367, thirteenth edition, 1906.

[134] Pesci: Gazzetta degli osped., vol. xxvii, p. 630, 1906.

H. C. Wood has long maintained that veratrum viride replaces bleeding advantageously, and that "the patient is bled into his own circulation" by it. In pneumonia, for instance, he deems it the best remedy at our disposal. This view is sustained by considerable clinical evidence. Gilardoni,[195] in an exhaustive experimental and clinical research, reached a similar conclusion. He found that the effect increased with the dose, but that it was more marked when the drug was given hypodermically. No other drug decreased the arterial tension with safety to such an extent. In one case, the patient took at one dose the entire quantity intended for twenty-four hours, and only showed as morbid symptoms vomiting and diarrhœa. J. B. Tuttle[196] also witnessed a case in which a man took by mistake, in the course of an hour, four teaspoonfuls of Norwood's tincture of veratrum viride instead of four drops. Some vomiting, slight pallor and marked weakness were the only symptoms observed.

Untoward Effects.—A large dose of veratrum viride brings out the physiological effects of veratroidine, an alkaloid present in too small a proportion in a therapeutic dose to provoke morbid effects. These occur in addition to a further depressing action upon the general vasomotor center and the resulting decline of arterial pressure, vomiting, diarrhœa, some hypothermia and cold sweating, all with feeble pulse and respiration.

These are the cases usually met with in practice. Besides the instances witnessed by Gilardoni and Tuttle, referred to above, cases have been reported in which the foregoing symptoms were present, by Pedigo,[197] Brothers,[198] and others. Wood[199] alludes to several instances in which teaspoonful doses of the fluid extract were followed by recovery. The other cases mentioned also recovered under appropriate treatment. In an experimental research, veratroidine was found by Wood[200] "to be more irritant than jervine, producing usually vomiting and some purging."

Acute Poisoning.—A poisonous dose of veratrum viride introduces new factors in the morbid process. By lowering the blood-pressure to an excessive degree, the blood is caused to accumulate in the large central vascular trunks, now widely dilated. This entails lowered oxygenation in all peripheral tissues,* as shown by the marked hypothermia present, and slowing of the blood-current in all organs. The functions of the pituitary body, including the adrenal center, being depressed from the same cause, less adrenoxidase is supplied to the blood—another feature that entails lowered oxygenation.* As a result of this, toxic waste-products gradually accumulate in the blood, and as such wastes violently stimulate the general vasomotor center, causing general vasoconstriction, the specific effects of the drug, vasodilation, suddenly disappear. These are soon replaced, however, by another cause of general vasodilation, *i. e.*, *inhibition* of the functions of the pituitary body and heart, due, as we have seen,[201] to excessive constriction of the arteries that supply these organs.[*]

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* *Author's conclusion.*

[195] Gilardoni: Gaz. Med. Italiana, Nos. 10, 11, 12, 1902.

[196] J. B. Tuttle: N. Y. Med. Jour., June 18, 1892.

[197] Pedigo: Va. Med. Mthly., Sept., 1889.

[198] Brothers: Mittheilungen des Vereins der Aerzte in Medicin, Oct., 1889.

[199] Wood: *Loc. cit.*, p. 370, thirteenth edition, 1906.

[200] Wood: Phila. Med. Times, Aug. 22, Sept. 12, 1874.

The transition stage from the legitimate effects of the drug to the phase of inhibition is marked by a clearly-defined sign: the pulse, previously soft and large and somewhat more frequent, now begins to drop steadily, until from perhaps 90, it falls to 50, 40, and even 30 per minute. This is due to the increasing pressure exerted by the blood-stream upon the heart.[*] Another result of the increasing vascular tension is violent retching and vomiting, due to the onslaught of blood in the gastric vessels, and the resulting reflex (vagal) action.[*]

The heart, whose work is markedly increased while its nutrition is reduced[*] (the ischæmia of the pituitary aiding the latter by depriving the blood of adrenoxidase[*]), soon begins to yield. While the period of inhibition is only in its incipiency, *i.e.*, while the heart's action is not very slow, its action may suddenly be rendered rapid, weak, and perhaps irregular by a physical exertion. Even in the absence of such an exciting cause, the organ soon assumes this gait—that of impending arrest. Relaxation of the vessels, due to loss of the propulsive power of the heart, now recurs. The blood once more receding to the deeper trunks,[*] the skin becomes cold, clammy, and bedewed with cold sweat, and the prostration is extreme. The brain likewise being deprived of much of its blood, vertigo, loss of vision, and unconsciousness occur in rapid succession. Finally, the pituitary and heart-muscle receiving an insufficient amount of blood to subsist,[*] the pulse becomes thready and then imperceptible, the heart ceasing its work in diastole. This is preceded, however, by arrest of the respiration, owing mainly to the fact that the venous blood is no longer projected with sufficient vigor to the pulmonary alveoli to be exposed to the air.[*]

Briefly, we have (1) recession of blood to the deep channels; (2) accumulation of hypocatabolized wastes in the peripheral and cerebro-central capillaries; (3) excessive excitation of the general vasomotor center and general vasoconstriction; (4) lethal vasomotor inhibition of the pituitary and heart.

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[*] *Author's conclusion.*

[201] *Cf.* this volume, p. 1185 *et seq.*

H. C. Wood,[illegible] many years ago, and again recently with H. C. Wood, Jr.,[illegible] found that when given hypodermically in toxic doses, veratroidine "caused an enormous rise of blood-pressure." This could not be ascribed to a direct action of the drug on the vasomotor center, but to deficient oxidation, since the author found that "it did not occur when artificial respiration was maintained"—a procedure which greatly increases the air intake. He ascribes it to "centric asphyxia," but we have seen that the phenomena ascribed to the inert CO_2 are in reality due to toxic waste products. Again, the cardiac inhibition was evidently the cause of the lethal phenomena, for H. C. Wood and H. C. Wood, Jr., referring to the former's earlier articles state that "in these it was noted that the veratroidine was an extremely powerful stimulant to the inhibitory nerves, so that it was possible to produce by it a cardiac arrest which was immediately put an end to by section of the vagi." Finally, if the lethal vasodilation is due to inhibition, and not to the vasomotor depressor jervine, a dose of the violent vasomotor stimulant veratroidine should counteract it. Wood states that "an animal, apparently dead, could be restored to life by vagal section, or by giving *more of the poison,*" referring to veratroidine.

The *treatment of veratrum viride poisoning* is described in a special section at the end of this volume.

Therapeutics.—In the incipient stage of *pneumonia* when excessive general vasoconstriction* tends to asphyxiate the patient by gorging his lungs with blood, veratrum viride in small therapeutic doses, given frequently until dyspnœa is relieved and the pulse is less tense, is a life-saving measure by causing general vasodilation and relieving the heart of undue resistance. It is of especial advantage in plethoric subjects. Veratrum viride is also of value in convulsive disorders, such as *puerperal eclampsia* and *epilepsy,* to prevent convulsions, which are due in part to excessive vasoconstriction and hyperæmia of the cerebro-spinal system.* It should be regarded only as a palliative, however, since it tends to encourage hypocatabolism and the accumulation of spasmogenic toxic* wastes in the blood. Veratrum viride is also of value in localized inflammatory processes such as *cerebritis, meningitis, pleurisy,* and *peritonitis,* to antagonize excessive hyperæmia. By causing general vasodilation it is also advantageous in *aneurism,* especially when there is danger of rupture.

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* *Author's conclusion.*

[illegible] H. C. Wood: Phila. Med. Times, Aug. 22, Sept. 12, 1874.

[illegible] H. C. Wood and H. C. Wood, Jr.: Amer. Jour. Med. Sci., May 9, [illegible].

ACONITE.

Physiological Action.—In therapeutic doses, aconite depresses the sympathetic center and causes general dilation of the arterioles.* An excess of blood being admitted into the capillaries, passive* hyperæmia is produced. Small doses infrequently repeated may thus cause a slight feeling of warmth; if frequently repeated, or if full doses are given, a characteristic symptom appears, viz., tingling, or prickling, felt at first either in the nose, lips, tongue, or finger-tips, and due to hyperæmia of the sensory terminals of the skin and mucous membranes.*

The prevailing view that aconitine causes the characteristic tingling by a local action of the remedy on the sensory terminals involves the assumption that—inasmuch as $^1/_{64}$ grain (0.001 gm.) of aconitine caused Dr. Meyer's death, and also that of a case reported by Lépine[illegible]—a solution of 1 in 8,000,000 (basing the calculation on only 16 pounds of blood and disregarding the lymph-vessels into which the plasma is constantly flowing) is the active factor in the process. Granting even that it has run safely the gauntlet of the antitoxic substances of the blood, this view does not appeal to reason. Especially is this the case when we take into account the fact that the tingling develops into hyperæsthesia, as it does at times in experimental animals, who jump about to avoid contact of their feet with the floor and show evidences of severe pain by their cries, and the fact that severe neuralgic pains occur in some cases of poisoning. These effects are obviously out of all proportion with the strength of the solution. On the other hand, we have a thoroughly logical explanation of these phenomena—and concurrently of all the other symptoms enumerated in the general text—in the sudden flooding of sensory elements with arterial blood. The dilation of the arterioles is generally recognized; Shoemaker,[illegible] for instance, states that "owing to the lowering of the blood-pressure and the dilatation of the arterioles caused by the aconite, the heat of the body is at first brought, with the increased blood-flow, to the surface."

Untoward Effects and Poisoning.—When a large dose of aconite or aconitine is taken, this passive hyperæmia provokes a sensation of warmth throughout the body, including the skin, mouth, pharynx, and stomach, and redness of the face. This is accompanied by the characteristic symptom, tingling, which may now spread over large areas—owing to flooding of the sensory terminals with adrenoxidase-laden plasma.* The nerves themselves, especially the upper division of the fifth pair, may also become hyperæmic,* and cause acute lancinating pain. Among other symptoms observed that are ascribable to this cause* are cephalalgia, tinnitus aurium, photophobia, dilation of the pupil, increase of cardiac power and of respiratory activity, salivation, nausea, vomiting, and pruritus.

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* *Author's conclusion.*

[illegible] Lépine: Semaine méd., vol. xii, p. 117, 1892.

[illegible] Shoemaker: "Therapeutics," sixth edition, p. 148, 1906.

Such a dose may introduce another morbid factor, *i.e.*, depression, then paresis of the test-organ, and through it of the adrenal center. The proportion of adrenoxidase being correspondingly reduced, general hypometabolism follows in all tissues, including the walls of the arteries and heart.

"In the very beginning of aconite poisoning," writes Wood, "the bodily temperature may rise slightly, but in severe poisoning a very pronounced fall occurs." The relationship of paralysis of the adrenal functions with this phenomenon is not only suggested by the rôle of their secretion in general oxygenation, but also by the concurrent "fall of the arterial pressure, which," as stated by Wood, "progressively increases to the end." Now, Strehl and Weiss[396] found that after removal of one adrenal, the blood-pressure fell 4 or 5 m.m. Hg., but that when the second adrenal was removed, the blood-pressure fell at once 20 or 30 m.m. and continued to fall till death ensued. Moreover, clamping of the adrenal veins—through which the secretion passes to the blood—caused the pressure to fall, while their release at once caused it to rise. What paralysis of the adrenal center means under such conditions is self-evident.

Several investigators, Boehm and Wartmann,[397] Guilland[398] and others hold that aconite causes a rise of the blood-pressure. But, as stated by Wood,[399] the stimulating action of the drug on the vasomotor system is not proved by their researches. Interpreted from my standpoint, these investigators observed the intercurrent rise which precedes convulsions. But as the latter are due to toxic waste products of hypocatabolism (owing to their imperfect elimination from the spinal system, an incident of the local ischæmia), we cannot incriminate the drug. Another misleading factor is the supposed physiological inhibition of the heart by the vagus. We have seen that this phenomenon is a morbid one, and that the nerves the vagus supplies to the heart are vasomotor. Hence the preliminary slowing by an excess of blood admitted into the heart and the subsequent tachycardia due to general vasodilation. (Marey's law).

When the dose is sufficiently large to prove fatal, the capillary hyperæmia is promptly succeeded by capillary ischæmia, caused by retrocession of the blood from all capillaries, and its accumulation in the deeper and widely dilated trunks, especially those of the splanchnic area.* This is due to the arrest of adrenal functions and the resulting depression of metabolic activity in the muscular layer of all vessels.*

This inaugurates the stage of general depression and finally collapse. The patient complains of great weakness, and of feeling cold and numb, the peripheral sensitive organs being now depleted of their blood. The surface is generally bedewed with sweat, the pupil is dilated, vision and hearing become impaired and towards the close may be lost, though the intellect remains clear.

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* *Author's conclusion.*

[396] Strehl and Weiss: Pflüger's Archiv, Bd. lxxxvi, S. 107, 1901.

[397] Boehm and Wartmann: Arbeit physiol. Würzburger Hochschule, Bd. i, S. 82, 1872.

[398] Guilland: Arch. de physiol. norm. et path., 2 série, vol. ii, p. 708, 1875.

[399] Wood: *Loc. cit.*, thirteenth edition, p. 382, 1906.

The pulse, at first slow, becomes rapid when the greater arteries are dilated (Marey's law).* Any exertion at this time, such as sitting up, etc., may cause cardiac arrest. The irregular action finally lapses into *delirium cordis,* and the heart's intrinsic circulation* soon becomes sufficiently reduced to paralyze its functions.

The respiration, slightly increased in activity at first, soon becomes slow and shallow, expiration being followed by a long pause. Cyanosis and other signs of asphyxia, often preceded by a feeling of tightness about the throat and convulsions, then appear, the precursors of death.

All this entails the conclusion that it is upon the centers that the drug acts. Laborde and Duquesnel,[310] Liégeois and Hottot[311] long ago furnished experimental evidence of this effect. Cushny[312] also refers repeatedly to a central action of the drug. Thus, he states that "the respiratory symptoms are certainly of central origin, though their explanation is still unknown." Again: "Death is due to paralysis of the respiratory center from the direct action of the poison." The "respiratory center" being, from my standpoint, the adrenal center, and the adrenals ceasing to produce their secretion, respiration becomes impossible. Cushny states that "the paralysis advances much more rapidly in the respiratory center than elsewhere, and death occurs from asphyxia." Cash and Dunstan[313] state that death in mammals is due "to central respiratory failure."

The *treatment of aconite poisoning* is described in a special section at the end of this volume.

Therapeutics.—Aconite has been used considerably for the arrest of *colds.* Its value in this connection is accounted for by the fact that it dilates the peripheral arterioles, and thus allows a greater volume of blood to penetrate the capillaries and to exercise more effectively its antitoxic action.* It is also beneficial in *neuralgia* and *migraine* when the blood-pressure is elevated, thus driving the blood into the diseased nerves;[*] under the influence of aconite the general lowering of the vascular tension, which the dilation of all the arterioles of the body entails,[*] thus relieves the pain.

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* *Author's conclusion.*

[310] Laborde and Duquesnel: "Des Aconits et de l'Aconitine," p. 108, 1883.

[311] Liégeois and Hottot: Brown-Séquard's Jour. de physiol., vol. iv, p. 520, 1861.

[312] Cushny: *Loc. cit.*, fourth edition, pp. 329 et seq., 1906.

[313] Cash and Dunstan: Proceedings Royal Soc. of London, vol. lxii, p. 338, 1898.

Aconite has been used in *sthenic pneumonia* to diminish the threatening asphyxia and relieve the heart, but veratrum viride is a better remedy for this purpose, since it depresses the vasomotor center[*] and relieves the pressure more effectually. It has been used in *fevers* of various kinds, but a better knowledge of the immunizing value of the febrile process has caused its use to be largely abandoned.

AMYL NITRITE.

Physiological Action.—Amyl nitrite, by stimulating the sensory end-organs of the fifth pair in the upper respiratory tract, while inhaled, causes reflexly a slight rise of the arterial tension by stimulating the sympathetic center;[*] but this effect is almost immediately replaced by general vasodilation beginning with the arterioles, due to the characteristic physiological effect of the drug: depression of the sympathetic center.[*]

Cushny[314] states that "in the beginning" and "from irritation of the nasal sensory terminations" . . . . . "the blood-pressure may rise and the heart be slowed from reflex action on the inhibitory and vasoconstrictor centers respectively." Reichert[315] also noted a primary stimulation. Wood[316] states that "our present physiological evidence justifies the belief that very small quantities of amyl nitrite primarily stimulate the heart, although it is demonstrated that in moderate or large amounts the drug respectively depresses or paralyzes the heart-muscle." Conversely, Vaquez[317] observed that a small dose inhaled by an individual whose arterial tension is moderate reduces the arterial tension by from 40 to 50 m.m. Hg., while a large dose lowers it by from 70 to 80 m.m. The primary stimulation is, therefore, but a preliminary incident due to the drug's irritating action upon the respiratory passages and independent, therefore, of its true physiological effect.

When a full or excessive dose of amyl nitrite is inhaled, the relaxation of the arterioles produced causes the capillaries of all organs, including the central nervous system, to become overfilled with arterial blood, *i.e.*, passively congested. The face, neck, and upper portion of the body become flushed; severe and sometimes violent headache, with confusion and perversions of color sense (objects appearing yellow), is complained of: the heart beats forcibly, the respiration is likewise accelerated and deepened. When moderate doses are used these phenomena gradually subside.

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[*] *Author's conclusion.*

[314] Cushny: *Loc. cit.*, fourth edition, p. 467, 1906.

[315] Reichert: N. Y. Med. Jour., July, 1881.

[316] Wood: *Loc. cit.*, thirteenth edition, p. 255, 1906.

[317] Vaquez: La presse méd., vol. ii, p. 702, 1904.

This stage of peripheral hyperæmia could not occur if the larger vessels, especially those of the splanchnic area, were likewise dilated, since the blood would accumulate therein, and cause ischæmia of the peripheral capillaries.* This is what takes place under the influence of large doses, those which likewise depress the vasomotor center. Another factor is superadded under these conditions, however: depression of the adrenal center either through direct depression of its functions or through ischæmia of the pituitary body.* The blood being thus rendered poor in adrenoxidase while the capillary streams are greatly reduced in volume, their blood is rapidly reduced, *i.e.*, rendered venous by the tissues.* Hence the fact that marked hypothermia and cyanosis occur under the influence of large doses.

The effects of the drug appear very promptly. Within a minute of the inhalation, according to Hale White,[228] the arterioles "may actually be seen to widen in the ear of a rabbit or in the retina." Similar observations have been recorded by Amez-Droz,[229] Gaspey,[230] Aldridge,[231] Bader and others. Francis Hare[232] also ascribes the action of amyl nitrite to "widespread, if not general, peripheral vasodilation," and holds that "this action is alone sufficient to explain the therapeutic effects which have been or may be observed in a number of clinically diverse affections." This is doubtless true in so far as the average dose is concerned.

The effects of large doses on the general blood-pressure are well shown in the following quotation: Nothnagel and Rossbach[233] state that the cutaneous vessels are not alone dilated; one may also see the vessels of the deeper organs, those of the pia mater, for example, are dilated, and may thus become twice or three times their normal diameter (Schüller, Schramm)." Cushny[234] states that both the arteries and veins are widened "very considerably under the influence of the drug," and that "the vessels of the abdominal organs and the brain are more affected than those of the extremities." Again, as will be shown under Nitroglycerin, dilation of the arterioles only does not cause an appreciable fall of the blood-pressure, while, as stated by Nothnagel and Rossbach, amyl nitrite may cause one of 50 m.m. and considerably below that as shown recently by Vaquez.[235]

The promptness with which cyanosis occurs is not fully accounted for by the cutaneous ischæmia, since other drugs which depress the vasomotor center do not produce this effect. The fact that the adrenal functions are likewise inhibited is suggested in various ways. According to Wood,[236] amyl nitrite "reduces most remarkably animal temperature"—as much as 13° F. (7° C.) in one of his experiments. Bourneville[237] observed in one of his experiments a reduction of 9° C. (16.2° F.). Wood ascertained that the excretion of carbon dioxide was reduced. The actual absence of a substance capable of taking up the oxygen of the air is shown by the fact that Gamgee[238] found "that amyl nitrite blood had lost its power of absorbing oxygen or of yielding oxygen to the air-pump." Devoid of adrenal secretion, the blood cannot absorb this gas, and what remained in it having been taken up by the tissues, none was available for the tissues.*

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* *Author's conclusion.*

[228] Hale White: "Materia Medica," London, 1892.

[229] Ames-Droz: Archiv de physiol., vol. v, p. 467, 1873.

[230] Gaspey: Virchow's Archiv, Bd. lxxv, S. 301, 1879.

[231] Aldridge: West Riding Lunatic Rep., vol. i, p. 71, 1871.

[232] Francis Hare: Clinical Journal, Aug. 29, 1906.

[233] Nothnagel and Rossbach: *Loc. cit.*, p. 406.

[234] Cushny: *Loc. cit.*, fourth edition, p. 465, 1906.

[235] Vaquez: *Loc. cit.*

Acute Poisoning.—The toxic effects are, in addition to the blood-changes described below, the cyanosis and the general vasodilation; excessive muscular weakness and great pallor, a slow, weak and irregular pulse, shallow and irregular respiration, loss of reflexes, wide dilation of the pupils, arrest of the respiratory movements, and asphyxia, sometimes preceded by tetanic convulsions.

All these effects are due to paralysis of the adrenal center.* Small doses obtund its sensibility temporarily; but poisonous doses paralyze its functions sufficiently to allow morbid changes to occur in the blood, which render it unsuitable for the continuation of life.*

The blood, under the indirect influence of toxic doses (in man) of amyl nitrite, assumes a nearly uniform chocolate-brown color, owing to the presence therein of methæmoglobin. This substance is hæmatin, the iron-laden constituent of hæmoglobin, which normally remains in the red corpuscles, and serves to hold therein the adrenoxidase (the albuminous constituent of the hæmoglobin molecule), pending its gradual distribution to the tissues. When, under the influence of amyl nitrite, too little adrenoxidase is available in the blood to supply the needs of tissue respiration, the hæmatin is not only deprived of the greater part of the adrenoxidase linked to it, but it is itself (in part), owing to its firm hold upon the last remnants of the latter substance, withdrawn from the red corpuscles into the plasma.* Hence the term "methæmoplasma." This symptom is not nearly as marked in man, however, as it is in animals.

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* *Author's conclusion.*

[236] Wood: *Loc. cit.*, thirteenth edition, p. 256, 1906.

[237] Bourneville: Cited by Manquat: *Loc. cit.*, vol. ii, p. 121.

[238] Gamgee: Philos. Trans. of Royal Soc. of London, vol. xvi, p. [illegible], 1868.

The usual picture of adrenal insufficiency promptly appears when the dose administered is excessive. "After poisonous doses," says Professor Wood, "the symptoms have been great pallor, usually dilatation, but sometimes contraction of the pupils, excessive muscular relaxation, slow, scarcely perceptible pulse, hæmoglobinuria and irregular respiration."

We have just seen that Gamgee found that amyl nitrite blood no longer yielded oxygen to the air-pump. Hammarsten[330] states that "methæmoglobin does not contain any oxygen in molecular or dissociable combination." The causative absence of oxidizing substance relegates the whole process of methæmoglobin formation to a corresponding diminution of oxygen, and invalidates the prevailing view that amyl nitrite and other drugs cause methæmoglobinæmia by acting directly on the blood.* Referring to a mouse killed in 2 minutes by amyl-nitrite inhalations, Haldane, Makgill and Mavrogordato[331] state that "the symptoms were those of asphyxia from *want of oxygen*." In another experiment the animal was placed in oxygen with a 0.3 c.c. capsule, and the oxygen pressure raised to 80 c.m. This mouse only died in 14 minutes. A third animal was placed in pure oxygen at atmospheric pressure and an 0.18 c.c. capsule. At the eleventh minute the air was removed; in a few seconds life had ceased. The blood in all was chocolate-colored. The authors also ascertained during experiments upon themselves that air deficient in oxygen or carbonic acid poisoning caused symptoms identical to those evoked by amyl nitrite. That methæmoglobin may be formed irrespective of any direct action upon it, and simply through abstraction of oxygen, is also shown by the following experiment, as described by Hammarsten: "If arterial blood be sealed up in a tube, it gradually consumes its oxygen and becomes venous, and by this absorption a little methæmoglobin is formed." Gamgee, however, found that the spectrum bands of methæmoglobin corresponded with those of *acid* hæmatin. "According to Rabuteau," writes Manquat,[332] "in animals poisoned with amyl nitrite, the blood becomes neutral and even acid." Again, if methæmoglobin is hæmatin *plus* a remnant of oxidizing substance, it should itself be reducible by the tissues after leaving the red corpuscles. The conversion into methæmoglobin "does not entail," says Cushny,[333] "the destruction of the red corpuscles, and the compounds are eventually *reduced* by the *tissues*, although the reduction progresses much more slowly than that of ordinary oxyhæmoglobin." Finally, Vulpian[334] found that in methæmoglobinæmia due to venom, the blood-corpuscles are almost all, when death did not occur promptly, deprived of their hæmoglobin. In the animal poisoned with amyl nitrite by Haldane, Makgill and Mavrogordato, the proportion of "hæmoglobin" converted varied from 80 to 92 per cent.

The *treatment of amyl nitrite poisoning* is described in a special section at the end of this volume.

Therapeutics.—The vasodilator action of amyl nitrite upon the arterioles, owing to the lowering of the vascular tension it involves, accounts for its beneficial action in *angina pectoris*, a disorder due to excessive arterial tension, and claudication of the heart. In the continuous hyperconstriction which keeps up the convulsions of *status epilepticus,* and the corresponding though temporary condition in *tetanus, puerperal eclampsia* and kindred disorders, the drug is of recognized value. An elevation of the blood-pressure, as will be shown, likewise prevails in *migraine* and *neuralgia,* a fact which accounts for the analgesic effect of amyl nitrite in this disorder. In *dysmenorrhœa,* the condition of the uterus and adnexa resembles closely that which prevails in angina pectoris; hence the benefit derived from the drug. In the *chill of intermittent fever,* due to hyperconstriction of the cutaneous arterioles, a few whiffs (about five minims) of amyl nitrite suffice to cause its cessation.

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* *Author's conclusion.*

[330] Hammarsten: *Loc. cit.*, p. 171.

[331] Haldane, Makgill and Mavrogordato: Jour. of Phys., vol. xxi, p. 160, 1897.

[332] Manquat: *Loc. cit.*, vol. ii, p. 121, 1903.

[333] Cushny: *Loc. cit.*, fourth edition, p. 468, 1906.

[334] Vulpian: C. r. de l'Acad. d. sci., vol. xciv, p. 612, 1882.

NITROGLYCERIN.

Physiological Action.—Nitroglycerin causes dilation of all arterioles,* by depressing directly the sympathetic center.* The capillaries of all organs being thus caused to receive an influx of arterial blood,* full therapeutic doses give rise to a sensation of fullness of the head with throbbing, more or less violent headache, vertigo, congestion of the conjunctiva, tingling or itching in the throat and tongue, salivation, muscular stiffness and spasmodic jerks, tinnitus aurium, flushing of the face and sometimes of the neck and trunk, and a feeling of constriction about the throat and precordial region. The cardiac contractions are more powerful, sometimes dicrotic, and, owing to the vasodilation, more frequent, the increased cardiac power extending up to and being discernible in the carotids.

Various investigators, including Hénocque,[335] Lauder Brunton and Tait,[336] and Hay[337] hold that nitroglycerin and amyl nitrite act similarly, notwithstanding the disparity in their chemical composition. The primary vasoconstriction due to irritation of the respiratory passages is not provoked by nitroglycerin, however, a fact ascertained experimentally by Haldane, Makgill and Mavrogordato.[338] Hence dilation of the arterioles is the first effect of the drug, irrespective of any intervention of the "inhibitory" or depressor mechanisms, which have introduced confusion in the study of amyl nitrite.

When the doses taken are administered too often, or when they are large, the dilation of the arterioles is supplemented by dilation of the larger vessels, caused by a similar depressing effect of the drug upon the bulbar vasomotor center and its subsidiary centers in the cord.*

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* *Author's conclusion.*

[335] Hénocque: C. r. de la Soc. de biol., 7 série, T. v, p. 669, 1883.

[336] Lauder Brunton and Tait: St. Bartholomew's Hosp. Rep., vol. xii, p. 146, 1876.

[337] Hay: Practitioner, vol. xxx, p. 422, 1883.

[338] Haldane, Makgill and Mavrogordato: *Loc. cit.,* p. 123.

The prevailing view is that nitroglycerin in therapeutic doses produces *general* vasodilation, but, as recently shown by H. P. Loomis,[illegible] such is not the case. By means of the sphygmomanometer used in a number of cases, some of which were observed until recovery, he ascertained that even when given in full therapeutic doses repeatedly, the drug did not lower the blood-pressure. It was only when given to dogs in doses which would have proved toxic to man that the blood-pressure fell, the heart being extremely weakened. The fall of pressure lasted only five minutes, however, though the heart remained feeble. The retrocession of blood from the capillaries was rendered evident by marked diminution of the volume of the kidney, as shown by an oncometer placed upon this organ.

This points clearly to the sympathetic center as the one depressed by the drug at first, since dilation of the arterioles *alone*, such as that produced by therapeutic doses, does not suffice to cause an appreciable fall of blood-pressure. Indeed, did such occur, there would not be flushing of the face and other signs of hyperæmia, but pallor and other signs of capillary anæmia, owing to recession of the blood to the deeper vessels. When large therapeutic doses are taken, however, the vasomotor center is also depressed by the drug. This is shown not only by the cardiac weakness in Loomis's dogs, and the dose required to produce it and reduce the pressure, but also, in man, by the fact that Von Noorden[illegible] found that by using very large doses, *e.g.*, "daily doses of 10 milligrams, and even 12 milligrams" ($^1/_6$ to $^1/_5$ grain), (the initial doses having been small and gradually increased) the blood-pressure could be reduced from 180 and 220 to 100 and 120, and even less, in his service in the Frankfort Hospital.

Untoward Effects and Poisoning.—The untoward phenomena produced by nitroglycerin are all those enumerated above which exceed a slight frontal fullness, tingling, itching, or formication in the throat and tongue and a slight quickening of the pulse, and, perhaps, a feeling of warmth about the face.

When the blood-pressure is reduced by depression of the vasomotor center, the arterial pressure falls and all the symptoms are those of collapse—the reverse of the erethic condition produced by the smaller doses, which affect only the sympathetic center. There is marked failure of the heart's action, and its beats may become weak, irregular and intermittent, the pulse being correspondingly feeble. The resulting retrocession of the blood from the surface, including that of the pulmonary alveoli, engenders inadequate oxygenation,* but another factor promptly aggravates the morbid process under these conditions: ischæmia of the anterior pituitary body and inhibition of the adrenal functions.* Hence the marked dsypnœa, hypothermia, anæsthesia, and cyanosis.

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* *Author's conclusion.*

[illegible] H. P. Loomis: Med. Rec., Mar. 18, 1905.

[illegible] Von Noorden: Verh. des Congress f. innere Med., Bd. xxi, S. 152, 1904.

The various stages of this process are explained in the foregoing general text.

The sequence of events caused by large doses may be illustrated by Demme's[341] experiments on himself with a 1 in 10 alcoholic solution. Two or three drops caused formication or itching (also mentioned by Vohl[342]) in the mouth and tongue, salivation, an increase of 10 to 12 beats in the pulse. After 6 to 10 minutes, dull, constrictive pains in the forehead, vertigo, cerebral fatigue. With *five* or *six* drops, these phenomena occurred sooner and were more marked; choreic movements of the masseter then appear, which may spread to other muscles when *ten* drops are given. Although these doses should not be taken as guide in practice, Loomis[343] states that the usual dose, $^1/_{100}$ grain (0.00065 gm.), is too small to produce any effect in pathological conditions, and that $^1/_{50}$ grain (0.0013 gm.) is a minimum dose. He regards it as a safe drug—in opposition to prevailing view—even large and repeated doses having never produced ill effects. D. D. Stewart[344] states that an excessive tolerance to nitroglycerin can be readily acquired if care is not taken to avoid a too rapid increase of the dose; hence the drug, though intelligently employed, is often of little service. He refers to a case in which 50 minims of a 10-per-cent. solution were taken daily without any very marked effects. Bins,[345] of Bonn, states that man "offers, as a rule, energetic resistance to nitroglycerin when the doses are not excessive," and refers to others who advocate larger doses than those generally administered.

Still we must not overlook the fact that nitroglycerin is capable of producing violent symptoms. Wood refers to an observation of Noer's,[346] in which ten-drop doses of an alcoholic solution (usually $^1/_{100}$) in a woman caused violent toxic phenomena.

The *treatment of nitroglycerin poisoning* is described in a special section at the end of this volume.

Therapeutics.—The beneficial effects of nitroglycerin are due to the fact that it lowers excessive arterial tension in the organs themselves, by dilating only the extremities of the vascular tree, *i.e.*, the arterioles.* In *angina pectoris*, for example, the pallor and ashen gray appearance of the surface observed not only during the paroxysm in some, but at all times, points to excessive vasoconstriction. Here, one minim of the 1-100 alcoholic solution, three times daily, suffices at first, but gradually, as the patient becomes habituated to the drug (the sympathetic center becoming less and less sensitive to its action*), it must be increased until three or four times the original dose is taken.

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* *Author's conclusion.*

[341] Demme: Cited by Albers: Deut. Klinik, Bd. xvi, S. 407, 1864.

[342] Vohl: Cited by Eulenburg: Berl. klin. Woch., Bd. ii, S. 251, 1865.

[343] Loomis: *Loc. cit.*

[344] D. D. Stewart: Jour. Amer. Med. Assoc., May 27, 1905.

[345] Bins: Revue de thérap. medico-chir., vol. lxxii, p. 656, 1905.

[346] Noer: Therap. Gaz., July 15, 1887.

The best rule for giving the drug for its effects on blood-pressure is, in Stewart's opinion,[247] to administer it four times a day in dose just sufficient to produce the slightest feeling of fullness in the head or to slightly quicken the pulse. If more than that is given, an undesirable tolerance is likely to be established. When a rather rapid increase seems needed to keep up a constant effect, it is best to discontinue the drug for two or more days, at intervals, and to resume its use with a smaller initial dose. By so doing the use of very large doses and strong solutions, which are not exactly safe to handle, will be avoided. Nitroglycerin, Stewart thinks, has not met expectations as a remedy in conditions of persistent high tension, and he now uses it in such cases less frequently than formerly, endeavoring at first, at least, to relieve by limiting the nitrogenous intake and maintaining free action of the skin and bowels. Aconite is often substituted for nitroglycerin in these cases with advantage.

It has been used to advantage in *epilepsy, puerperal eclampsia,* and kindred disorders in which the arterial tension is high. This phenomenon is also present in *uræmia.*

DRUGS WHICH RESEMBLE NITROGLYCERIN IN THEIR PHYSIOLOGICAL ACTION.

Erythrol tetranitrate is somewhat less active than nitroglycerin, but its effects endure much longer and begin earlier after its ingestion. Its physiological action differs in no way from that of nitroglycerin. Being also a violent explosive, tablets should alone be prescribed.

CREOSOTE, CREOSOTE CARBONATE, GUAIACOL AND GUAIACOL CARBONATE.

Physiological Action.—Creosote is primarily a depressant of the sympathetic and vasomotor centers.* If the patient be markedly asthenic, as the result (1) of the disease from which he is suffering; (2) of a congenital hypersensitiveness of the two vascular centers mentioned;* (3) of a temporary hypersensitiveness of these centers, brought on by shock, pain, etc., even a small dose may provoke sufficient general vasodilation* to cause an accumulation of blood in the great central vessels, and by depleting the peripheral vessels cause marked hypothermia.

This is a very important feature of the action of creosote, which should be borne in mind when it is prescribed in tuberculosis. Its depressing action on both vascular centers is illustrated by its effects on the temperature. Thus R. Simon[248] states that in some subjects, hypothermia lasts as long as creosote is employed; in one of his cases it remained 1.1° C. (2° F.) below normal during the two months that it was used. Burlureaux[349] states that after injections of creosote "the patient may complain of a most unpleasant sensation of internal cold; his extremities are icy, and his lips cyanosed. . . . ." Desplats[350] found that, like guaiacol, it caused "a general and intense vasodilation with all its consequences." Even a small dose may cause death under such conditions. Zawadzki[351] reported a death in a young woman who was taking 18 minims daily.

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* *Author's conclusion.*

[247] Stewart: *Loc. cit.*

[248] R. Simon: "Créosote Tolérance et Intolérance," Paris, 1[illegible].

The production of a temporary vulnerability of the vascular centers to the morbid effects of creosote is well shown by various instances reported by Simon. In several cases "the drug was tolerated perfectly before and after an attack of influenza, but not during this disease." In another, large doses could be taken excepting during menstruation. In some, the untoward effects came only after the injections had caused severe pain. In one of Burlureaux's cases, it came on immediately after a painful traumatism, etc. That advanced cases of tuberculosis cannot bear creosote, and that certain persons are very susceptible to its effects, is well known.

When marked general asthenia is not present, the arteries and arterioles are only sufficiently dilated to admit a greater volume of blood than usual into all capillaries,* and to reduce excessive vascular tension. This action is supplemented by another which endows creosote with its curative properties in appropriate cases, viz., it excites a protective reaction of the test-organ.* The adrenal center being stimulated, the quantity of adrenoxidase in the blood is increased and its proportion of auto-antitoxin likewise.* The volume of arterial blood circulating in the capillaries—of the lungs, for example—is thus not only increased, but its bacteriolytic and antitoxic properties are also enhanced.

Arloing[352] found that creosote, as well as eucalyptol, guaiacol and mercury, when injected repeatedly into goats, caused their blood to acquire the property of "agglutinating rapidly and completely Koch's tubercle bacilli suspended in homogeneous emulsions." He found that in equal volume this goat serum "agglutinated somewhat less energetically than the serum of goats which had received tuberculin." The connection between this condition of the blood and the preliminary depression of the vascular centers produced by the drug is illustrated by the *hyper*thermia which occurs when the *hypo*thermia ceases. Thus, Simon states that in cases of intoxication the temperature becomes steadily lower until the seventh hour, when (under the influence of the adrenoxidase, which has been accumulating all this time*) a reaction occurs, the temperature gradually rising up to 39° C. (102.2° F.) or 40° C. (104° F.), the latter coinciding with free sweating. This indicates, as Desplats says, "a sudden and general vasoconstriction, which should not be considered as a sign of intoxication. Indeed, such a reaction is the sign of recovery even after enormous doses, as shown by several cases on record. In a case of Faisans's[353] a dose of 9.5 gms. (146 grains) taken surreptitiously by the patient to hasten his cure, the hypothermia was succeeded by a temperature of 38° C. (100° F.) and hyperæsthesia, showing that the peripheral capillaries were hyperæmic.

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* *Author's conclusion.*

[349] Burlureaux: "Traitement de la Tuberculose par la Créosote," 1894.

[350] Desplats: Jour. des sc. méd. de Lille, vol. xvii, pp. 1, 25, 1894.

[351] Zawadzki: Centralbl. f. innere Med., Bd. xv, S. 401, 1894.

[352] Arloing: C. r. de l'Acad. des sc., T. cxxvi, May 9, 16, 1898.

[353] Faisans: Bull. gén. de thérap., Feb. 8, 1896.

Untoward Effects and Poisoning.—As shown by the above analysis, the untoward symptoms are due to depression of the sympathetic and vasomotor centers,* and the resulting general vasodilation. The blood accumulating in the deeper vessels, the subjective signs are progressive hypothermia with sensation of intense cold, cold sweats, contracted pupil, vertigo, marked adynamia, cyanosis, and unconsciousness with involuntary emesis and micturition—on the whole a cholera-like syndrome—due to ischæmia of the peripheral organs. In markedly debilitated individuals collapse may occur, and death follow respiratory failure.

In the majority of cases, however, after a period of six or seven hours, the drug is sufficiently modified by the blood's auto-antitoxin* (especially adrenoxidase, which by oxidizing it turns it black*) to lose its depressing power over the vascular centers,* and the tide turns. The blood-vessels not only resume their normal caliber, sometimes suddenly, but the reaction of the test-organ, which the presence of the drug in the blood has excited all along,* having caused overactivity of the adrenal center and, as a result, an accumulation of adrenoxidase in the blood,* evokes the hyperthermia referred to, which may reach 104° F. (40°C.). The cutaneous and cerebro-spinal vessels being now overfilled with blood, general hyperæsthesia, hallucinations, talkative delirium, dilation of the pupil, restlessness and trismus may occur. The urine is usually smoky, owing to its content in oxidized creosote*—the oxidation* continuing in some instances when the urine is exposed to the oxygen of the air. The patient soon recovers completely.

The untoward effects are not necessarily caused by large doses only. Simon refers to cases in which doses as small as $^1/_{15}$ minim (0.0012 c.c.) and 5 minims (0.3 c.c.) brought them on. It depends entirely upon the condition of the patient, *i.e.*, from my standpoint, of the sensitiveness of his vascular centers. In such cases these centers are on the verge of collapse, and this may occur in persons who have been taking the drug right along, owing, we have seen, to the debilitating action on the patient's *sensorium commune* of some intercurrent influence, menstruation, grippe, pain, etc. Neither sex nor age influences the production of these phenomena. Lamplough,[234] who treated 100 cases without meeting with untoward effects, gave children from two to five years of age 30 minims (2 c.c.) daily. He followed strictly a rule which should never be set aside when creosote is used, viz., to begin with very small doses so as to test the patient's sensitiveness. Schoull[335] used it safely in patients ranging from two months old to ninety-one years of age. This does not mean that extreme ages are free from its toxic effects. Marcard[336] observed a fatal case of poisoning in an infant four weeks old, in which the most prominent symptom was cyanosis.

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* *Author's conclusion.*

[234] Lamplough: Brit. Med. Jour., May 28, 1898.

The identity of creosote as a derivative of wood-tar accounts for the fact that it may become oxidized in the blood. Wood[337] states, in fact, that "it occurs in the urine probably in part as oxidized educts." We have seen that, as shown by Bertrand, Loew and many others, plants contain a ferment which becomes oxidized and black on exposure to oxygen. That the process of distillation liberates such a ferment is probable. Simon, referring to instances of poisoning, states that "the urine may be already black on leaving the bladder, or it may blacken very rapidly on being exposed to the air." This suggests that the vegetable ferment might prove active in the blood, but many facts indicate that such is not the case.

The *treatment of creosote poisoning* is described in a special section at the end of this volume.

Therapeutics.—*Creosote carbonate* which contains ninety per cent. of creosote is preferable to pure creosote. It is an oily, tasteless liquid which can be readily administered in capsules. In *lobar pneumonia* creosote is of very great value during the early stages, when the diseased area is engorged. A dangerous feature of this stage is the excessive vascular tension. The drug not only counteracts this condition, but it opens the channels through which the auto-antitoxin-laden blood can penetrate to the diseased lobes.* The pneumococcus being readily killed, creosote often becomes a life-saving measure. This applies as well to *broncho-pneumonia*. In *pulmonary tuberculosis*, the slight vasodilation produced likewise enables the arterial blood laden with antitoxin to reach more freely the diseased portions of the lung,* and thus to enhance the local reparative process. The manner in which it is to be used is indicated under the headings of these various disorders.

Guaiacol may be used instead of the foregoing, but the *guaiacol carbonate* is less toxic and should be given the preference. A curious property of guaiacol is to produce, when painted on the skin, a more or less marked hypothermia. It does this by depressing reflexly the vasomotor and sympathetic centers.*

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* *Author's conclusion.*

[335] Schoull: Jour. des praticiens, vol. xi, p. 373, 1897.

[336] Marcard: Vjhrsch. f. gericht. Med. u. S., Supp.-Hft., S. 20, 1889; Schmidt's Jahrbücher, Bd. ccii, S. 269, 1889.

[337] Wood: *Loc. cit.*, thirteenth edition, p. 842, 1906.

Vasodilation thus produced is of advantage as an emergency measure, as will be shown, but not in the treatment of the disorders in which, on the other hand, creosote and creosote carbonate are of great value.*

Carbolic acid acts much as does creosote, but it is more active as a stimulant of the adrenal mechanism, and the depressing action on the sympathetic and vasomotor centers is antagonized almost from the start by a large increase of adrenoxidase.* Toxic doses, however, likewise paralyze the vascular centers, and produce marked hypothermia. The internal use of carbolic acid is especially interesting on account of Baccelli's success with it in *tetanus*. His results are accounted for by the fact that, the proportion of auto-antitoxin in the blood being greatly increased by the drug, the spasmogenic poison is actively destroyed.*

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* *Author's conclusion.*

CHAPTER XXII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PHARMACODYNAMICS (*Continued*).

THE BLOOD-PLASMA OF TERRESTRIAL ANIMALS AS THE FUNCTIONAL HOMOLOGUE OF SEA-WATER.

The kinship between the blood-plasma of vertebrates and sea-water was referred to in the first volume. I wrote at the time:[1] "The many vestigial structures which the human frame exhibits as relics of its evolutional past not only include evidences of a primitive aquatic existence, the embryonic branchial or gill-clefts and the pituitary bodies, for instance; but the plasma in which all the cells of the organism bathe may be said also to typify the original medium." Since then, the question has received considerable attention, as shown by the quotations submitted below, which indicate that the subject as a whole harmonizes perfectly with the soundest teachings of many branches of science.

René Quinton, who pointed out this similarity between sea-water and the blood-plasma, in 1900 at the XIII International Congress, more recently presented the results of additional investigations before the Paris Academy of Sciences. "In M. Quinton's view," says a correspondent,[2] "sea-water is the natural source from which, as Haeckel believes, those elementary bodies have their rise, which in turn develop into every other species, human beings included. The environment in which the anatomical elements of living creatures exist is neither more nor less than a marine one. Our tissues and cells continue to exert their functions in a fluid the composition of which presents the closest resemblance to that of sea-water. Hitherto the number of elements entering into the composition of a living body has been considered to be about fifteen. But the researches of M. Quinton have shown the existence of traces of at least some fourteen other elements which are also found in sea-water, such as copper, lead, silver, gold, and others. Further, if an animal be bled to exhaustion and the place of the blood be supplied by sea-water, on the morrow the animal will have regained its strength, and at the end of five days its recovery is complete. M. Quinton has injected into animals a quantity of sea-water greater than their own body weight without any toxic effects, whereas an injection of pure water brings about death. Sea-water then appears to be the nutrient fluid of animals, their natural plasma in fact."

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[1] *Cf.* vol. i, p. 788, 1903.

[2] Paris Correspondent: Lancet, Apr. 16, 1904.

Other observers have lately taken up the question. Macallum, of Toronto,[3] finds from geological evidence "that in the ocean of the earliest period the relative proportions of the elements: sodium, potassium, calcium and magnesium approximated to those found in river discharges or in fresh water shed from areas covered with archæan rocks. This condition must have continued until living forms made their appearance in the ocean, when the gradual elimination of the magnesium, and particularly of the potassium and calcium, began. The living forms were in all probability unicellular; and 'as the period must have been of great duration, the organisms and their protoplasm acquired a fixed relation to the four elements.' In the transition from the ocean of the more ancient composition to that of the present, the unicellular forms became multicellular, and developed circulatory systems, the vascular fluids of which were at first simply modified sea-water. Professor Macallum lays stress on the resemblance between the blood-plasma of vertebrates and sea-water as regards the relative proportions in which sodium, potassium and calcium are present, and considers this similarity to be due to heredity, 'the proportions of the saline constituents of the plasma being a reproduction of the proportions which obtained in sea-water when circulating plasmata were developed.' He thinks the same general principle holds good for protoplasm as well, and maintains that both animal and vegetable protoplasm derive their relations to the elements, sodium, potassium, calcium and magnesium, from the composition of sea-water which obtained when all forms were unicellular."[4]

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[3] Macallum: Trans. Canadian Institute, p. 181, vol. 1903-4.
[4] Editorial: Brit. Med. Jour., July 9, 1904.

The researches of Jacques Loeb,[5] and the investigations of Matthews, Fischer and others, have also shown that "the solution which is most favorable to the life of the tissues is one which contains a number of salts, and these in the same concentration in which they exist in sea-water. The excess, deficiency or removal of one or more of these salts disturbs the equilibrium of the solution, which becomes toxic for the animal cell. The practical application of this fact is obvious. The normal salt solution of the future will be one having practically the same composition as sea-water, if not sea-water itself.

"It is easy to explain the reason for this predilection of the animal cell for an environment having the same saline content and concentration as the water of the ocean. During the dawn of life all cells lived amid this environment, and the chemical and physical structure of protoplasm became adapted to the chemical and physical characteristics of the surrounding medium. In spite of the enormous lapse of time, and the complex elaboration of the simple protoplasmic units into the higher animal forms, the former still retain the ingrained habits of their primitive life."[6]

Professor Bunge, of Basle,[7] states that he is "convinced that the remarkably high percentage of salt in vertebrate animals, as well as the desire to take salt with our food, can only be satisfactorily explained by the theory of evolution." He also remarks in this connection: "The land vertebrates are all remarkably rich in salt, in spite of the scanty supply around them. But even these are only apparent exceptions. We need but remember the fact that the first vertebrates on our planet all lived in the sea. Is not the large amount of chloride of sodium found in the present inhabitants of dry land another proof of the genealogical connection, which we are forced to accept from morphological facts? There is no doubt that each of us in his individual development has gone through a stage in which he still possessed the chorda dorsalis and the branchial arches of his sea-dwelling ancestors. Why may not the high average of salt in our tissues be also inherited from them?

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[5] Jacques Loeb: Pflüger's Archiv, Bd. cvii, S. 252, 1905.

[6] Editorial: Med. News, Sept. 9, 1905.

[7] Bunge: "Physiologic and Pathologic Chemistry," Eng. Trans. by Starling, pp. 101, 102, 1902.

"If this interpretation be correct, we should expect that the younger the vertebrates are in their individual development, the more salt they would possess. This is in fact the case. I have convinced myself by numerous experiments that an embryo of a mammal contains more salt than a new-born animal, and that it gradually becomes, after birth, poorer in chlorine and sodium as it develops. Cartilage contains the most sodium of any tissue in our bodies, besides being also the tissue of greatest antiquity. It is histologically identical with the tissue which still survives in the skeleton of the Selachians, a sea-water animal, during its whole life. The human skeleton, as every one knows, is originally also composed of cartilage, and even before birth much of this is replaced by bone. This phenomenon cannot be understood on teleological grounds; it can only be explained by the theory of evolution."

These quotations—purposely used to preserve the full force of the evidence they contribute—indicate how far-reaching was Claude Bernard's conclusion[8] that the blood is "an internal medium in which anatomical elements live as do fishes in water." Indeed our own bodies are but colonies of aquatic animals, of unicellular organisms that live precisely as do unicellular organisms in their primordial habitat, the seas. Here these minute cells absorb their food from the surrounding medium; they assimilate it and reject their wastes as do our cells in the lymph of the intercellular spaces. Immobilized, however, when, as cell-colonies, they constitute organs, they are unable to provide for themselves; we have seen how Nature meets the needs of this new state of things: even in the lowly sponge, free amœboid cells, leucocytes, act as food-purveyors—the type of the nutritional process (as interpreted from my standpoint) in all multicellular organisms, including our own. In the lower form the amœboid messengers gather the food-stuffs from the marine medium; in the higher, they collect them from the alimentary canal. But the walls of this identical channel, where antecedent living matter is taken up to be carried where it will again assume the living state, are the seat of another phenomenon: the absorption of water which, with what salts the food. contains—sodium chloride mainly—serves to elaborate the original fluid in which our "anatomical elements can live as do fishes in water," and differing only from that of the ocean, as to constituents, in that it courses in canalicular systems.

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[8] Claude Bernard: "Leçons sur les propriétés des tissus vivants," pp. 55-58, 1866.

It would appear as if, gradually as the cells are grouped into increasingly complex colonies until an organization such as that of man is reached, their chances of life should be correspondingly reduced. Especially does such a conclusion seem to impose itself when we realize that long before the higher mammals are reached, the preservation of the living state depends upon a multitude of factors; that the structure as a whole is disposed into organs having totally different functions, secretory, contractile, nervous, etc., which in turn are disposed into systems whose functions include chemical processes of various kinds, respiratory, digestive, excretory, etc. Yet such does not appear to be the case under normal conditions, *i.e.*, when the physiological functions of even the higher animal are carried on in accord with provisions of Nature. The normal longevity of the parrot, of the elephant, of man and other animals attests to this: it affords proof that increased complexity does not entail increased vulnerability. The reason for this becomes apparent when function is reduced to its simplest expression in the light of my own views: whenever an exacerbation of activity becomes manifest, it is always evoked by an increased flow of an oxygen-laden fluid whose physical and chemical properties are those of the sea, around cells specifically disposed to determine the function. Even the nerve-cell with its elongated axis-cylinder, its tufts of dendrites, the minute fibrils that connect it with other cells, the neuroglia, etc., (as I interpret them) are channels for the adrenoxidase-laden plasma analogous, as to its qualitative attributes, to the primordial seas —a small cosmos, it is true, but a cosmos nevertheless.

If a living muscle, a nerve, etc., be immersed, as was done by Overton,[9] in solutions of various salts, a striking fact asserts itself, viz., that the nearer the composition of sea-water is approached, the longer does the organ preserve its functional activity. Need we wonder that the effect of saline solution, which, injected into our tissues, meets therein all the other salts of sea-water, should, as another editorial writer[10] says, be "little short of miraculous?" It is but a bit of the ocean that the moribund receives, but to his cell—marine-cells—it is the one medium compatible with life.

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[9] Overton: Pflüger's Archiv, Bd. cv, S. 176, 1904.

MARINE SALTS AS ACTIVE PARTICIPANTS IN THE BODY'S DEFENSIVE FUNCTIONS.

The defensive properties of all the body fluids, the blood, lymph, serum, etc., including the digestive ferments of phagocytes, can only be exercised efficiently when the alkalinity of these fluids is adequate.* When, owing to the presence of a pathogenic substance, a toxin, a poison, toxic wastes, etc., the proportion of auto-antitoxin is augmented in the blood,* the alkalinity of the latter must increase proportionally; otherwise the bacteriolytic and antitoxic action of the antitoxin is inhibited* and the defensive process is weakened in proportion.

The alkalinity of the blood, lymph, etc., is due to the presence of *sodium and potassium phosphates,* which are intimately associated, and generally referred to as the "alkaline phosphates." Closely associated with these salts are the *alkaline carbonates* (sodium carbonate and bicarbonate, and potassium carbonate). They assist the former in giving the blood and lymph their alkalinity, but they also enable the plasma to absorb carbonic acid from the tissues and to eliminate this gas. After fulfilling their functions the alkaline phosphates are excreted in the perspiration and urine: about 4.5 gms. (68 grains) being eliminated in the latter daily by a normal adult.

The relationship of the blood's alkalinity to the defensive functions of the body has been urged by several experimenters. Charrin[11] gives the blood's alkaline reaction the first place in the immunizing processes of the body. It increases leucocytogenesis, and, therefore, the number of phagocytes available. Löwy and Richter[12] noted that the leucocytes increased in number in proportion as the alkalinity became more marked. We have seen that trypsin is the active proteolytic agent in the germicidal and antitoxic substance—including Buchner's alexin. Metchnikoff[13] states that alexin "acts only in the presence of salts. When relieved of its salts by dialysis, the serum loses its hæmolytic power, but as soon as these salts are restored to it, this power reappears." As (in the light of my views) these same defensive substances are the active agents in tissue metabolism, a corresponding relationship between this process and the blood's alkalinity should exist. Gautrelet[14] noted an absolute parallelism between metabolism and the alkalinity of the blood, *i.e.*, nutrition was found low when the alkalescence was low, and *vice versa*, both in man and in the lower animals. The blood's alkalinity is intimately related with the energizing agent in auto-antitoxin, namely, adrenoxidase. Thus, while Orlowsky[15] found that the alkalinity of the blood in various diseases is proportionate with the number of red corpuscles, declining when these are few and increasing as their number increases (the leucocytosis influencing the alkalinity in no way), Mylius[16] found that, although the red corpuscles themselves were neutral or acid, the *blood-platelets* were strongly alkaline. Now, I have shown[17] that these platelets were droplets of adrenoxidase.

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* *Author's conclusion.*

[10] Editorial: Medicine, Sept., 1901.

[11] Charrin: "Les défenses naturelles de l'organisme," 1898.

[12] Löwy and Richter: Virchow's Archiv, Bd. cxlv, S. 49, 1896.

[13] Metchnikoff: "L'Immunité dans les mal. infectieuses," p. 93, 1901.

The experimental application of these facts in infection proves their importance. The researches of Behring and Nissen,[18] for example, concluded that the resistance of the white rat to anthrax was due to the intense alkalinity of its blood. Paul found that when the alkalinity of the rabbit's blood was neutralized, its germicidal power disappeared. Calabrese[19] found that the alkalinity of the blood increased with the degree of immunization, and that the blood reacted against a toxic by a steady increase of alkalinity. In comparative experiments in a large number of animals, von Fodor[20] found that their resistance to the anthrax, cholera, tubercle and streptococcus inoculations was greatly increased when sodium bicarbonate was administered, either subcutaneously or orally.

Sodium Chloride, though a neutral salt, is a most important inorganic constituent of the body fluids: Owing to the smallness of its molecules (58.5) and its chemical inertia, it is preëminently the salt which maintains the osmotic equilibrium between the tissues and the blood. When the supply is inadequate, all the functions are hampered, since it is the solvent of adrenoxidase* (serum globulin). By holding the latter in solution it insures its free circulation as a constituent of the plasma in all vessels down to the minutest capillary networks distributed to cellular elements, including those of the nervous system: the axis-cylinders and other neuro-fibrils, the networks of neurons, their dendrites, etc.* This also enables the adrenoxidase-laden* plasma to transude freely through the capillary walls in order to reach the tissue-cells, *i.e.*, to carry on the life process. The free osmotic properties which the lymph in the tissue-spaces also owes to sodium chloride insures another important function, viz., that of sweeping away by the lymph-current of all wastes derived from the cell.

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* *Author's conclusion.*

[14] Gautrelet: Arch. gén. de méd., Mar. 27, 1906.

[15] Orlowsky: Deut. med. Woch., Bd. xxix, S. 601, 1903.

[16] Mylius: Cited by Labbé: Presse méd., vol. ix, p. 989, 1902.

[17] *Cf.* vol. i, p. 715, in the first three editions, and this volume, p. 828.

[18] Behring and Nissen: Zeit. f. Hygiene, Bd. viii, S. 412, 1890.

[19] Calabrese: La semaine méd., vol. xv, p. 467, 1895.

[20] Von Fodor: Centralbl. f. Bakt. u. Parasit., Bd. xvii, S. 225, 1895.

The influence of sodium chloride on osmosis is so well known that evidence to that effect is not required. The extent to which it enhances the efficiency of the protective processes in infection may be illustrated by a few examples. Lubomoudrov[31] found that a saline solution composed of 0.5 per cent. of sodium chloride and 1 per cent. of sodium sulphate in distilled water, injected intraperitoneally or subcutaneously, caused leucocytosis and increased phagocytosis. They retarded the development of typhoid and cholera bacteria, and in some instances caused its destruction. Prophylactic injections, given twenty-four hours before inoculation, enabled guinea-pigs to resist a dose from two to three times as large as that which killed controls. It becomes a question, however, which of the two salts mentioned insured these results. It is evidently not the sodium sulphate, for *sodium and potassium sulphate*, though found in practically all the fluids of the body and eliminated at the rate of about 4 gms. (60 grains) daily in the urine, are in reality but excretory products derived from the oxidation of proteids and other organic substances containing sulphur.

Conversely, a multitude of clinical facts on record—some of which will be submitted later—have shown that sodium chloride in "decinormal saline solution" produces precisely the effects noted by Lubomoudrov.[32]

Experimental researches point in the same direction. Lesné and Richet, Jr.,[33] for instance, found that if, after injecting a solution of potassium iodide into two dogs, sodium chloride solution was also injected in the blood of one of the dogs, toxic phenomena came on in the latter only after 1.16 gm. (17 grains) per kilo of animal had been given, whereas in the dog deprived of the saline they appeared when 0.32 gm. (5 grains) per kilo had been reached. Ercklentz[34] also found that animals given fatal doses of a toxic and saved by saline solution, showed little pathological trace of the intoxication when killed, while animals left to die, *i.e.*, without saline solution, showed marked histological alterations. F. J. Bosc and V. Vidal,[35] in fact, ascertained experimentally that the solution of sodium chloride and sodium sulphate, equal parts (7 per mille), did not present any difference in results from those of the ordinary saline. Their researches imposed the conclusion that simple saline solution of the above strength possesses the minimum of harmful effects and the maximum of physiological effects, and should be the solution of choice for massive intravenous injections.

Therapeutics.—*Sodium chloride* is a potent adjunct in many morbid processes, especially in *febrile diseases*, because it maintains the fluidity and circulatory freedom of the autoantitoxin-laden plasma.* It insures the access of the plasmatic adrenoxidase to the diseased area and, owing to the thyroidase it contains, it sensitizes (as opsonin) the bacteria, detritus, etc., thus facilitating their ingestion and destruction by the phagocytes.* It also enables these cells, as well as the leucocytes, which supply nucleo-proteid granules and trypsin to the plasma, to migrate freely to the exposed region and carry on their protective function efficaciously.[*]

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* *Author's conclusion.*

[31] Lubomoudrov: Annales de l'Inst. Pasteur, vol. xix, p. 573, 1905.

[32] Lubomoudrov: *Ibid.*

[33] Lesné and Richet, Jr.: Progrès méd., Mar. 28, 1903.

[34] Ercklentz: Therapie der Gegenwart, Jan., 1903.

[35] F. J. Bosc and V. Vidal: Arch. de physiol., 5 série, vol. viii, p. 937, 1896.

Over one-half ounce of sodium chloride being eliminated daily with the urine, the sweat, fæces, etc., the reduced diet and the anorexia prevent, especially during febrile diseases, its being replaced through its normal source, the food.[*] The body's supply becoming inadequate very soon, the protective functions are hampered in proportion as the deficiency of the salt is marked.[*] *This is a fruitful cause of death in all infections.*[*]

This applies as well to the *alkaline salts,* the elimination of which proceeds at the rate of about 68 grains daily in the urine alone. Gradually as their proportion in the blood becomes reduced, both the nutrition of the body and the activity of its defensive process, plasmatic and cellular, are correspondingly inhibited, irrespective of the remedies administered.[*]

In accord with the teachings of physiology, Hutchison[36] states that the considerable increase of alkalinity during the ingestion of food is synchronous with the appearance of the "alkaline tide in the urine." He explains this alkalinity, at least in part, "by the absorption of alkaline salts from the food." The quantity thus eliminated is very large. Thus Halliburton[37] says of sodium chloride (common salt), that "about 16 gms. (247 grains) are daily excreted in the urine, and smaller quantities in the sweat and fæces." Halliburton also says in this connection that "during its passage through the body, it facilitates the absorption of proteid food, and increases tissue metabolism." This applies as well to morbid states. Thus, Fornaca and Micheli[38] found that the physiological salt solution increased nutrition in convalescents, and the proportion of red corpuscles. The anorexia and reduced nutrition which accompany febrile diseases necessarily follow from the well-known fact mentioned by Labbé[39] that during digestion the alkalinity decreases, while it is lowered during fasting.

In diseases in which the intake of food is reduced, the proportion of the various salts in the blood should not, as is now the case, be taken as guide for the elaboration of artificial sera, since the excretion of these salts with, or as, wastes, does not correspond with this proportion.[*] The aim should be to compensate for the salts of which the body is deprived through the reduced diet, to enable it to carry on its bacteriolytic and antitoxic functions to the best advantage.[*] *To neglect this factor in a febrile case is to compromise the issue.*

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[*] *Author's conclusion.*

[36] Hutchison: Lancet, Mar. 7, 1896.

[37] Halliburton: Schäfer's "T. B. of Physiol.," vol. i, p. 77, 1898.

[38] Fornaca and Micheli: Riforma medica, vol. xviii, ii, p. 374, 1902.

[39] Labbé: Presse médicale, Oct. 18, 1902.

Since I urged in 1903,** the importance of supplying the patient in all febrile diseases, *from the beginning*, the salts he fails to receive owing to the reduced diet which his sickness entails, a number of clinicians have carried out this plan, as to the sodium chloride, with marked advantage, as will be shown under "Treatment" of the various diseases in which this measure is indicated. J. B. Todd, of Syracuse, having found that saline solutions were as effective when used as beverages, as when given subcutaneously or by enema, while J. Madison Taylor, of Philadelphia, found that the ordinary saline solution tablets fulfilled the object admirably for the preparation of the beverages, there is no ground, on the plea of complicated technique, to deprive the patient of a measure which *in acute fevers is of greater importance than any drug.*

On the whole, the proportion of sodium chloride and alkaline salts to be administered should correspond with the diminution of nourishment which the disease, in one way or another, entails.* If the patient receives in the twenty-four hours one quarter of his usual food, the salts given should be three-quarters of the quantities excreted, taking into account size, sex and age; if the food-intake is reduced only one-half, but one-half of the salts excreted are necessary, etc. The proportions would then be as follows:—

An adult man taking in 24 hours	Sodium Chloride	Sodium Phosphate
¾ Food	60 grains (4 gms.)	15 grains (1 gm.)
½ "	120 " (8 ")	30 " (2 gms.)
¼ "	180 " (12 ")	45 " (3 ")
0 "	240 " (16 ")	60 " (4 ")

These salts may be added to the milk, broths, or other beverages and foods. It is most important that the patient should drink water freely, especially in febrile processes, to preserve the normal specific gravity of the blood and other fluids. This serves also to insure a low specific gravity of the urine, notwithstanding the free elimination of acids and other wastes, thus protecting the kidneys.

When the salts cannot be administered entirely by the mouth, they should be given by enema, and, if necessary, subcutaneously or endovenously, injecting in the latter cases the classic saline solution—approximately one teaspoonful (or more exactly, 69 grains) of common salt to one pint of sterilized water at *not less* than 110° F.—and *very slowly.* It does not itself raise the temperature, as is now taught: it enables the blood suddenly to resume its antitoxic functions, the hyperthermia being but an expression of the life-saving process.*

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* *Author's conclusion.*

** *Cf.* vol. i, p. 787, in the first three editions.

For hypodermoclysis or intravenous injection the plain saline solution is the most satisfactory and safest. The addition of *sodium bicarbonate*, recommended by some, tends to cause local gangrene, as shown by Baish[31] and others, but this salt may be given advantageously by the mouth when there is acidosis. Another salt, *sodium sulphate*, appears in many foreign formulæ, but, as we have seen, it is a waste-product and useless. *Calcium*, which, according to Howell, Jacques Loeb and others, stimulates the heart, is eliminated in such small quantities that it need not be replaced. It tends, in fact, to promote the formation of emboli. *Potassium*, as shown by Loeb, Matthews, Fischer and others, prolongs cellular life; but a very minute quantity suffices for this purpose, and as milk contains potassium chloride, it supplies the needs of the body. The precautions to be observed in injecting saline solution are the following: The solution and apparatus should be sterilized, and the skin be thoroughly cleansed at the place of injection. The temperature should be 110° to 115° F. The passage of air into the tissues or vessels should be avoided. Never more than half a pint should be injected in one place in the cellular tissue. The infusion should be carried out slowly; about one ounce a minute can be safely introduced into the veins or the subcutaneous tissue.

Contraindications and Untoward Effects.—The contraindications are self-evident: if there exists any œdema, pericardial, pulmonary, peritoneal, etc., especially if this is due to renal disorder, the addition of a large quantity of fluid and a marked increase in the osmotic property of all body fluids will naturally increase the trouble. When nephritis is present, the enhanced metabolic activity which saline solution causes will aggravate the renal disorder by increasing the waste-products. When the patient is liable to hæmorrhages, pulmonary, uterine, cerebral, etc., to increase the osmotic properties of the blood will augment the danger. In arteriosclerosis, cardiac degeneration, etc., they are believed to be dangerous, but evidence to this effect is lacking.

The latter belief is based on the mistaken theory that the solution distends the arteries, but Sollmann[32] found that intravenously injected solutions of sodium and potassium disappeared in great part from the circulation *per se* and passed into the tissues by physiological filtration as injected, then out with the urine. Even large quantities failed to augment the fluid contents of the vessels. J. B. Briggs[33] ascertained sphygmomanometrically that "it is useless to infuse with any idea of filling up the depleted vessels [in shock]; the water and salt are excreted probably quite as rapidly as they pass into the circulation."

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* *Author's conclusion.*

[31] Baish: Deut. med. Woch., Sept. 4, 1902.

[32] Sollmann: Archiv f. exper. Path. u. Pharm., Bd. xlvi, S. 1, 1901.

[33] J. B. Briggs: Johns Hopkins Hosp. Bull., Feb., 1903.

The supposed untoward effects are really not such.* As previously stated, the elevation of temperature produced is not due to a direct action of the saline solution, as now believed: it is due to the fact that the blood is enabled by it to resume its bacteriolytic and antitoxic functions, a process which entails a rise of temperature.* The rise of vascular tension is but a normal outcome of this process, the muscular coat of all vessels and the cardiac muscle itself being also the seat of enhanced metabolic activity.* The glycosuria is also but a proof that the adrenal system itself is suddenly liberated,* since we have seen that adrenal extractives provoke glycosuria.

REMEDIES USED TO INFLUENCE SPECIAL ORGANS.

All remedies acting, in the light of my views, through one or more nerve-centers, no drug ingested and absorbed from the alimentary canal, or administered subcutaneously, intravenously, etc., should act specifically upon any one organ without influencing others in the same way. This fact is emphasized by the physiological effects of the drugs analyzed below—which are usually referred to as "local remedies."

Purgatives are shown to act in various ways. The first of these is by their direct irritating action on the intestinal mucosa, which causes its glandular elements and the organs forming part of the digestive system to increase their activity reflexly. Here the drug is not absorbed, however; it acts precisely as would an irritant applied to the conjunctiva. An important feature is illustrated in this connection, viz., that the main action of purgatives is to provoke an increase of auto-antitoxin in the intestinal fluids which tends to asepticize the contents of the canal. It applies as well to purgatives, such as mercury, which are absorbed, since, as we have seen, this metal stimulates powerfully the adrenal mechanism and enriches all secretions in auto-antitoxin.

Emetics may likewise act as local stimulants, the irritation of the gastric mucosa causing vomiting reflexly, as is well known. Others, apomorphine, for instance, are shown to produce the same effect in another way: they depress markedly the sympathetic and vasomotor centers, and cause such marked general vasodilation through relaxation of their walls that blood enters freely into all glandular elements. Those of the gastric mucous membrane, among others, becoming hyperæmic, a condition similar to that produced by direct irritants, such as mustard, is awakened, and vomiting occurs.

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* *Author's conclusion.*

Diaphoretics differ from emetics in that they depress the sympathetic center only. All arterioles being dilated, an influx of blood occurs into all glandular capillaries, including those of the sweat-glands. Whereas emetics cause passive hyperæmia only, diaphoretics cause local increase of function, owing to the normal condition of all vessels except the arterioles. The secretory activity of the sudorific glands, among others, is therefore markedly raised, and sweating occurs.

Oxytocics, of which ergot is the main type, produce their effects by stimulating actively the vasomotor center. They thus drive a large amount of blood to the various organs, including the uterus. The contractile power of the uterine muscle being thus greatly enhanced, it responds with correspondingly greater energy to the periodical impulses it receives during parturition. The influence of oxytocics on hæmorrhage is due to this potent constrictor action on the smaller vessels governed by the vasomotor center; but the fact that blood is forced peripherally by these drugs renders them dangerous for this purpose.

Diuretics.—These agents are shown to produce their effects in various ways. Saline solution, for instance, indirectly enhances metabolism through its influence on osmosis. An excess of waste-products being produced, the kidneys are caused reflexly to increase the excretory activity—a process aided by the excess of water introduced into the blood. Digitalis also causes diuresis by increasing metabolism, since we have seen that it stimulates the adrenal mechanism. Mercury, another diuretic, is also, as shown, a powerful adrenal stimulant. These remedies all raise indirectly the vascular tension—an active factor in the production of diuresis.

PURGATIVES.

Physiological Action.—Most purgatives increase the secretory activity of the intestinal glands by causing irritation of the intestinal mucosa, *i.e.*, by augmenting reflexly the local blood-supply through the vagus, the stricto-dilator nerve* of the alimentary system. As the intestinal juice, owing to the presence therein of adrenoxidase (secretin), nucleo-proteid (which with adrenoxidase forms enterokinase), and pancreatic juice, including trypsin, all of which jointly form auto-antitoxin, the physiological purpose of this increase of secretion is evidently a protective one, viz., to rid the intestine of an irritating substance.* If this canal happens to contain pathogenic organisms, toxins or other harmful substance, they are likewise exposed to the action of the auto-antitoxin in the intestinal juice. This is one of the most important functions of the intestinal juice, and the therapeutic value of purgatives is mainly due to the fact that they accentuate the efficiency of this function.*

Thiry[34] found that slight mechanical irritation, as tickling with a feather, sufficed to cause an exposed area of the mucosa of the small intestine to secrete. The influence of local irritation is further shown by the fact that in herbivora, the large proportion of refuse or residuum left in the intestine causes the stools to be loose, while in carnivora they are habitually dense, with a tendency to constipation. Thiry failed to increase the secretory activity of the intestinal mucosa by the local application of purgatives, but several other observers have obtained positive results. In accord with Moreau,[35] Vulpian,[36] for example, found that a solution of magnesium sulphate or jalap injected into the small intestine caused a local catarrhal congestion with the effusion of much fluid, which was found to contain red corpuscles and leucocytes. Lauder Brunton[37] also found that Epsom salt, gamboge, elaterium and croton oil stimulated the secretory activity of the small intestine. Manquat[38] states that all the experiments performed to demonstrate that irritation was produced could be summarized as follows: when an exposed coil of small intestine was ligated in four places a few inches apart, thus forming three segments, the injection of a cathartic substance into one of the three caused this segment alone to become filled with liquid. H. C. Wood, Sr. and Jr.,[39] state (1906) that "the evidence, both experimental and clinical, is indeed overwhelming in favor of increased secretion."

That the secretory activity of the intestinal mucosa is due to nervous action, and that the secretory nerve is the vagus, is shown by the fact that H. C. Wood, in 1870, found that division of the vagus on both sides, in the neck, prevented the action of purgatives. Vulpian,[40] as a result of the experiments recited above, concluded that the increase of secretion produced by the local irritation of cathartics was due to reflex action.

The presence of the various constituents of what I have since termed "auto-antitoxin" in the intestinal juice was shown in the fourteenth chapter,[41] to which the reader is referred.

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* *Author's conclusion.*

[34] Thiry: C. R. de l'Acad. de méd., vol. xlvi, 1868.

[35] Moreau: *Ibid.*, July 5, 1870; Sept. 12, 1871.

[36] Vulpian: Gaz. méd., vol. xliv, p. 300, 1873.

[37] Lauder Brunton: Cited by Wood: *Loc. cit.*, thirteenth edition, p. 645, 1906.

[38] Manquat: "Thérapeutique," vol. i, p. 677, 1903.

[39] Wood, Sr. and Jr.: *Loc. cit.*, thirteenth edition, p. 646, 1906.

[40] Vulpian: *Loc. cit.*

[41] *Cf.* this volume, p. 850.

Another prominent physiological effect of purgatives is to increase the peristaltic movements of the intestines, in addition to their stimulating influence upon the secretory activity of the intestinal mucosa. Saline purgatives do not increase intestinal peristalsis, however, when given in therapeutic doses—an important practical fact when it becomes necessary to asepticize by purgation* and flush the intestinal canal without increasing the movements of its walls, as during the onset of peritonitis, appendicitis, etc.

Nothnagel and Rossbach[62] conclude that "the principal cause of purgation lies in an increase of the peristaltic movements of the intestine." The experiments of Legros and Onimus,[63] Houckgeest[64] and others have shown, however, that this does not apply to saline purgatives. Vulpian, in the course of the experiments referred to above, found, in fact, that while jalap and other vegetable cathartics increased peristalsis, the salines did not. Radziejewski[65] found that purgatives in general increased the peristaltic movements of the small and large intestine, but that it was mainly by enhancing those of the colon that the alvine dejections were rendered more frequent. Lauder Brunton teaches that there can be no doubt as to the fact that purgatives increase both the secretory activity and the peristaltic movements of the intestine. Wood, Sr. and Jr.,[66] adduced a number of facts which are, they state, "incompatible with any other belief than that purgatives cause both increased secretion and increased peristalsis in the alimentary canal." Experimental evidence shows clearly, however, that an exception must be made as to the salines.

Mercurial purgatives do not produce their effects through either of the two mechanisms described above.* After being taken up from the intestinal canal they act as ordinary drugs by exciting the test-organ, and through it the adrenal center.* By thus increasing the proportion of adrenoxidase in the blood, they raise the secretory activity of the pancreas and of the intestinal glands by enhancing their intrinsic metabolism.* They also augment the proportion of adrenoxidase that traverses the liver, this substance appearing in the stools as biliverdin and giving them the familiar green color.* Mercurial purgatives enhance the bacteriolytic antitoxic properties of the blood (especially in the liver), besides that of the intestinal canal.*

The physiological action of mercury was reviewed at length under the heading of that drug, to which the reader is referred. We have seen that mercury, even when rubbed into the skin, sufficed to provoke violent irritation of the intestinal mucosa and diarrhœa by increasing excessively the proteolytic property of the blood. This shows that primary contact is not a *sine qua non* of purgation. Podophyllotoxin was *found by* Neuberger[47] *to* purge when given hypodermically and to cause intestinal hyperæmia. Apocodeine, introduced by Guinard, has also been found effective as a cathartic, when given subcutaneously, by Raviart, Heinze[48] and others. These, and other agents used in a similar way, markedly irritate the tissues at the site of injection and are used no longer. It is probàble that all cholagogues act much as do the mercurials, by a central action, but no evidence to that effect is available.

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* *Author's conclusion.*

[62] Nothnagel and Rossbach: *Loc. cit.*, p. 564, 1880.

[63] Legros and Onimus: Jour. de l'anat. et de physiol., vol. vi, pp. 37, 163, 1869.

[64] Houckgeest: Archiv f. d. ges. Physiol., Bd. vi, S. 266, 1872.

[65] Radziejewski: Arch. f. Anat., S. 37, 1870.

[66] Wood, Sr. and Jr.: *Loc. cit.*, thirteenth edition, p. 646, 1908.

Therapeutics.—*Castor oil* acts mildly as a stimulant of the intestinal mucosa, when therapeutic doses are used, though quite active as a purgative. It provokes just enough local hyperæmia to enhance the germicidal and antitoxic activity of the intestinal fluids.* Hence* its value in *diarrhœa* and *dysentery* due to the presence of pathogenic organisms. It is, in fact, effective in all mycotic disorders of the alimentary canal, especially in children. In the *bronchial catarrh* of infants it is very efficacious as revulsive.

Croton oil, owing to the violence with which it acts, in very small quantities, is of great value as a drastic purgative in *apoplexy, acute mania, uræmic coma,* etc. By causing a copious outpour of intestinal fluid, it relieves the blood-pressure. In *impacted fæces*, or *intestinal obstruction,* the large quantity of fluid with which the canal is flushed increases materially the chances of recovery. In *lead colic* it is especially advantageous, owing to the rapidity of its action.

Salines.—These salts include sodium sulphate, magnesium sulphate, magnesium citrate, potassium tartrate and bitartrate, and potassium and sodium tartrate. Of these the citrate and sulphate (Epsom salts) are of especial value in inflammatory disorders of the abdomen, *peritonitis, enteritis* and threatening *appendicitis,* and in many *acute fevers,* not only because they do not cause peristalsis while flushing the bowel, but also owing to the intestinal antisepsis they tend to promote.* The purgative mineral waters, Seidlitz, Hunyadi Janos, Friedrichshall, Pullna, etc., owe their properties mainly to magnesium sulphate.

Mercurials.—The therapeutic value of mercurials in this connection was reviewed in the article on Mercury.

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* *Author's conclusion.*

[47] Neuberger: Archiv f. exper. Path. U. Pharm., Bd. xxviii, S. 32, 1891.

[48] Heinze: Psychiat-neurol. Woch., Bd. v, S. 297, 1903.

The numerous other purgatives at our disposal present nothing of special interest in connection with the internal secretions, other than those referred to under "Physiological Action."

EMETICS.

Physiological Action.—Certain emetics, such as mustard and zinc sulphate, produce their effects by irritating the gastric mucosa. Afferent impulses being transmitted to the vagal center (in the posterior pituitary body*), the various muscles, gastric and thoracic, which take part in the act, are reflexly stimulated, and the irritant is vomited.

When such emetics as ipecac and apomorphine are employed, they are absorbed, and produce their effects by depressing the functional activity of the sympathetic and vasomotor centers.* All arterioles and larger arteries being relaxed, the glandular elements of the entire body are passively congested and secrete vicariously.* The passive congestion of the gastric mucous membrane being supplemented by a more or less great outpouring therein of serous pseudo-secretion,* the same process that prevails when irritants are ingested occurs, *i.e.*, the stomach is emptied through reflex vagal action.

Although emetics which are first absorbed, ipecac, apomorphine, etc., appear to influence only the stomach and the muscles that the act of vomiting brings into play, such is evidently not the case. Manquat,[49] for instance, states, referring to tartar emetic, "a dose of 0.01 gm. ($^{1}/_{6}$ grain) causes nausea, a general malaise, salivation, exaggeration of the gastro-intestinal secretions, and at the same time sweating and exaggeration of the bronchial secretion."' He states also[50] that ipecac causes prostration, coolness of the skin, salivary hypersecretion, sweating, "hypersecretion of all the glands of the digestive apparatus (liver, pancreas, mucous follicles), this giving rise to a moderate diarrhœa." Even the nasal secretion is increased. Wood[51] states that the vomiting caused by apomorphine is accompanied by "excessive secretion from the salivary, nasal and lachrymal glands." It is evident, therefore, that emesis is but one of the phenomena awakened by an emetic, and that these agents, as do most drugs, produce their effects by acting upon a center. Indeed, Wood[52] distinguishes emesis produced by local irritation of the stomach (mustard, sulphate of zinc, etc.) from that of "centric" origin. Gianuzzi[53] found that after the cervical portion of the spinal cord had been divided in the dog, tartar emetic failed to produce emesis. Foulkrod[54] obtained the same result with emetin, the active principle of ipecac.

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* *Author's conclusion.*

[49] Manquat: *Loc. cit.*, vol. i, p. 575, 1903.

[50] Manquat: *Loc. cit.*, vol. i, p. 288, 1903.

[51] Wood: *Loc. cit.*, thirteenth edition, p. 640, 1906.

[52] Wood: *Loc. cit.*, thirteenth edition, p. 632, 1906.

[53] Gianuzzi: Cited by Manquat: *Loc. cit.*, vol. i, p. 577, 1903.

[54] Foulkrod: Phila. Med. Times, vol. viii, p. 551, 1878.

That it is the vascular centers, *i.e.*, the sympathetic and vasomotor centers, which are influenced by this class of drugs, and, moreover, that it is by depressing these centers that emesis is caused, is shown by the fact that the blood-pressure is markedly lowered by ipecac, as observed by Pécholier,[55] Reboul,[56] Podwyssotzki,[57] Grasset and Amblard[58] and others, as well as by apomorphine as shown by Harnack[59] and Reichert.[60] The concomitant hypothermia which occurs under such conditions through recession of blood from the surface is likewise present. Thus, Radziejewski[61] found that the temperature could drop 6.6° C. (11.8° F.). Hayem[62] observed that in the rabbit 0.005 gm. ($^{1}/_{12}$ grain) brought the temperature down 1° C. (1.8° F.) in one hour. Manquat states that emesis is usually attended with a fall of 1° C. Apomorphine does likewise, according to Nothnagel and Rossbach,[63] the temperature declining "little by little."

The rôle of the vagus as the direct factor in the production of emesis is well shown by the fact that, as stated by Manquat, "the experiments of Chouppe, Polichronie and Dyce Duckworth have shown that emesis does not take place when emetine is injected after division of both vagi." The fact that emesis occurs while the emetic is being eliminated by the gastric membrane (Radziejewski) being also established, we have three sources of irritation of the vagal sensory terminals in the gastric mucosa: passive congestion, the serous secretion, and the excreted (and probably chemically transformed) emetic.

Untoward Effects and Poisoning.—Toxic phenomena may be produced by emetics, especially in infants, feeble and aged subjects, the symptoms being those of collapse, with marked muscular weakness and a steady lowering of the temperature. This is due to increasing paresis of the sympathetic and vasomotor centers.* In apomorphine poisoning, unconsciousness, failing respiration, and profound depression and convulsions (due to accumulation of toxic wastes*) are the main symptoms, death being due to asphyxia.

Both the sympathetic and vasomotor centers being depressed, accumulation of blood in the great vessels of the splanchnic area occurs. This is shown by the fact, "attested by Pécholier, Dyce Duckworth and d'Ornellas, that in emetine poisoning, although there is a distinct fall of temperature in the mouth and on the surface of the body, in the intestine the temperature remains stationary, or more commonly rises." Wood[64] also states that "Dyce Duckworth especially noted intense hyperæmia of the lungs, which were in some places emphysematous, but in other portions collapsed"—the typical *passive* hyperæmia of sympathetic paralysis. The recession of blood from the periphery produced by large doses is also well shown by Wood's additional statement that Magendie and d'Ornellas had "also seen cases in which ischæmia of the pulmonary tissue was found after death."

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* *Author's conclusion.*

[55] Pécholier: Gaz. méd., vol. xxxiii, p. 744, 1862.

[56] Reboul: Cited by Manquat: *Loc. cit.*, vol. i, p. 589, 1902.

[57] Podwyssotzki: *Ibid.*, p. 589.

[58] Grasset and Amblard: Montpellier méd., vol. xl, pp. 101. 197, 293, 1881.

[59] Harnack: Archiv f. exper. Path. u. Pharm., Bd. iii, S. 44, 1875.

[60] Reichert: Phila. Med. Times, vol. x, p. 109, 1879.

[61] Radziejewski: Arch. f. Anat. u. Physiol., S. 472, 1871.

[62] Hayem: Cited by Manquat: *Loc. cit.*, vol. i, p. 581, 1902.

[63] Nothnagel and Rossbach: *Loc. cit.*, p. 726, 1889.

[64] Wood: *Loc. cit.*, thirteenth edition, p. 637, 1906.

There is considerable analogy between the action of emetics as described above, and that of hypnotics, previously submitted. Tartar emetic and other emetics have long been known to possess soporific properties. C. J. Douglas[**] has shown recently that this applied also to apomorphine.

Therapeutics.—*Ipecac* as an *emetic* is given to adults in 20-grain (1.3 gm.) doses, repeated at intervals of twenty minutes if necessary. In children 5-grain (0.3 gm.) doses suffice. Its action is aided by drinking lukewarm water freely. The value of ipecac in *dysentery* is accounted for by the fact that by enhancing vicariously the activity of all glands, including the pancreas and intestinal glands, it increases the sterilizing properties of the succus entericus.[*] This serves not only to destroy pathogenic organisms that may be present, but also to hasten the resolution of lesions of the mucosa—a process further aided by the local hyperæmia awakened. In *hæmoptysis* it acts very favorably by diminishing general blood-pressure,[*] even when given in small doses. In *chronic bronchitis,* the same mechanism and the fact that it increases the secretory activity of the bronchial mucosa renders it particularly effective where the secretion is viscid and raised with difficulty, notwithstanding hard and exhausting paroxysms of cough.

Apomorphine as an *emetic* may be given hypodermically to adults in $^{1}/_{10}$ grain (0.006 gm.) doses at fifteen minutes interval until vomiting occurs, reducing the dose in weak or aged subjects. It may be given in larger doses by the mouth. In a child of eighteen months $^{1}/_{50}$ grain (0.0013 gm.) and in one of eight years $^{1}/_{25}$ grain (0.0026 gm.) suffice. In the cough of *bronchitis* it is of marked value in small doses, repeated every three hours, to increase the bronchial secretion and hasten the process of resolution. In *hysteria,* it is of great value to counteract the muscular rigidity by relaxing the arterioles.[*] The hyperæmia of the central nervous system being also relieved,[*] the patient falls into a refreshing sleep.

DIAPHORETICS.

Physiological Action.—The physiological action of diaphoretics is well exemplified by *jaborandi* and its alkaloid, *pilocarpine.*

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[*] *Author's conclusion.*

[**] C. J. Douglas: N. Y. Med. Jour., Mar. 17, 1900.

These agents produce sweating by depressing markedly the sympathetic center.* The diaphoresis represents only, however, an epiphenomenon of the effects of jaborandi, all glands being affected in the same manner as the sweat-glands.* The depression of the sympathetic center, by causing dilation of the arterioles of all these organs, causes functional hyperæmia of their capillaries;* hence the increase of secretory activity. Hence also* the flushing of the face, the salivation, lachrymation and, in some instances, the diarrhœa and vomiting observed.

That sweating is but one of the phenomena of a drug which affects all glands as well as the sweat-glands is sustained by considerable evidence. Thus, Tzistovitch[66] ascertained experimentally that pilocarpine stimulates *gastric* secretion, and that the gastric juice appears early in proportion as the dose is large. Edkins[67] and Masloff[68] found that pilocarpine administered caused *intestinal* secretion. Heidenhain[69] found that it caused intense secretory activity in the crypts of the colon. This applies to the muscular coat as well. Morat[70] and others have found that it caused very active peristalsis in experimental animals. Bayliss and Starling[71] note that pilocarpine increased the *pancreatic* secretion, the latter being rich and thick. In all cases the gland seemed to tire rapidly and to become insusceptible to the drug. Lauder Brunton and Delépine[72] found that pilocarpine stimulated glandular activity of the liver-cells. It increases the functional activity not only of the sweat-glands, but also of all cutaneous glands. Thus, Langley[73] observed that in the frog the skin became covered with a thick, viscid secretion.

That these phenomena are due to depression of the sympathetic center is suggested not only by the facial hyperæmia, but also by the nausea and vomiting which, as I have shown, are due partly to sympathetic depression. Even the average dose may cause these symptoms. Thus, H. C. Wood,[74] referring to the effects of a therapeutic dose of the infusion of jaborandi, states that "there is not rarely nausea, and sometimes vomiting," of "large quantities of glairy mucus" he adds elsewhere in his text. Again, the increased functional activity of various organs provoked points in this direction. Horbaczewski,[75] for instance, found that pilocarpine produced, in man, a leucocytosis, and a proportionate increase in the uric acid excretion, a fact which shows that general metabolism is increased. Again, Murrell observed that in the frog, 1/20 grain (0.003 gm.) of pilocarpine gave rise to a marked increase of reflex activity and convulsion—phenomena which point to excessive hyperæmia of the skin and central nervous system. Even the nerves are hyperæmic. C. R. Marshall,[76] in the course of experiments with pilocarpine, noted that it increased the sensitiveness of the vagus to electrical stimulation. Finally, that it is by causing *dilation* of the arterioles that pilocarpine causes sweating is shown by the fact, demonstrated by Langley[77] in 1875 and confirmed since by many observers, that absolute antagonism exists between this drug and atropine. Now, as I have shown, atropine *constricts* the arterioles.

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* *Author's conclusion.*

[66] Tsistovitch: Bolint Gazeta Botkina, July 13, 1902.

[67] Edkins: Schäfer's "T. B. of Physiol.," vol. i, p. 555, 1898.

[68] Masloff: Untersuch. a. d. physiol. Inst. d. Univ. Heidelberg, Bd. ii, 1882.

[69] Heidenhain: Hermann's "Handbuch," Bd. v, i, S. 171, 1883.

[70] Morat: Lyon méd., vol. xl, pp. 289, 335, 1882.

[71] Bayliss and Starling: Jour. of Physiol., vol. xxx, p. 61, 1903.

[72] Lauder Brunton and Delépine: Proceed. of the Royal Soc. of London, vol. lv, p. 424, 1894.

[73] Langley: Jour. of Physiol., vol. i, p. 339, 1878.

[74] H. C. Wood: *Loc. cit.*, thirteenth edition, p. 721, 1906.

[75] Horbaczewski: Bull. du Comité agric. du Départ. de l'Aube, France, B. 100, Sect. 3, p. 101, 1892.

[76] C. R. Marshall: Jour. of Physiol., vol. xxxi, p. 120, 1904.

The peripheral hyperæmia is augmented through the fact that the arterioles of the adrenals are relaxed, as are those of all other glands, and that the increase of adrenal secretion produced causes general vasoconstriction, the blood being driven towards the periphery, *i.e.*, the skin.[*]

The prevailing belief that pilocarpine increases the activity of all the glands of the body, including those of the skin, by acting *directly* upon them, is, to say the least, illogical when we consider that $^1/_8$ to $^1/_4$ grain (0.008 to 0.016 gm.) will produce marked effects. The only proof of any weight, the fact that Luchsinger,[78] and subsequently Nawrocki, found that division of the nerves of a cat's leg did not prevent the paws from sweating when jaborandi was injected into the animal, fails when analyzed from my standpoint. All the vessels of the leg being dilated by the section of the vasomotor nerves, any general rise of the blood-pressure would cause a flood of blood to invade these dilated vessels and the sweat-glands, and provoke sweating. Now, Wood, alluding to Reichert's[79] experiments, states that "immediately after the injection of the alkaloid [pilocarpine] into the jugular vein the arterial pressure falls, but in a few moments the characteristic phenomena of a slow pulse with *increased arterial pressure* come on." It becomes a question, however, as to how this rise of pressure is produced, but we have the solution of this problem in the fact that A. Pettit[80] found the adrenals greatly congested and swollen in experimental animals poisoned with jaborandi. As this means hyperactivity of these glands, and as the adrenal secretion raises the blood-pressure, not through the vasomotor center, but, as I have shown, by enhancing metabolic activity in the muscularis of all vessels the cause of the rise of blood-pressure is self-evident.

Untoward Effects and Acute Poisoning.—The symptoms which follow a toxic dose include the following: copious sweating, vertigo, marked salivation, rhinorrhœa, vomiting, diarrhœa, strangling, dimness of vision, myopia, more or less marked cardiac oppression and metrorrhagia—all due to what amounts to paralysis of the arterioles.[*] Sudden death has also been produced by a small dose ($^1/_3$ grain—0.021 gm.) pilocarpine given hypodermically. As it is the sympathetic center which is depressed by this drug,[*] it should be given with especial care in debilitated and aged subjects.

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[*] *Author's conclusion.*

[77] Langley: Brit. Med. Jour., Feb. 20, 1875.

[78] Luchsinger: Archiv f. d. ges. Physiol., Bd. xv, S. 482, 1877.

[79] Reichert: Univ. Med. Mag., Apr., 1893.

[80] A. Pettit: C. r. de la. Soc. de biol., vol. iii, p. 536, 1896.

Lanphear[31] recommends caution in the use of pilocarpine. Its continued use may also give rise to papulo-exudative dermatoses. Thus, in a case observed by Hallopeau and Vielliard,[32] the histological examination revealed an inflammatory exudate about the excretory ducts of the sweat-glands.

Therapeutics.—*Jaborandi and Pilocarpine.*—The latter drug is to be preferred, since it is less likely to provoke vomiting. It has been found of value in *uræmia, chronic Bright's disease* and *dropsical conditions*; the benefit is due to the lowering of the blood-pressure which general dilation of arterioles insures,* and to the increased elimination of fluids and retained excrementitious wastes. It is of use in *erysipelas*, owing to the fact that the cutaneous hyperæmia means the presence in the affected area of an increased volume of auto-antitoxin.* *Chronic eczema* and other cutaneous disorders, especially those due to deficient secretion of the sweat-glands, are also improved by pilocarpine. In ophthalmic disorders associated with *intra-ocular pressure,* it is also valuable, owing to the general lowering of the blood-pressure it insures.* In *orchitis* it tends, through the same process,* to relieve the intense pain.

Sweet Spirit of Nitre.—This agent, an alcoholic solution of amyl nitrite, acts, as does pilocarpine, by depressing the sympathetic. It is milder, however, and acts both as diuretic and diaphoretic. It is considerably used in *febrile disorders* of children when excitement, startings, etc., occur. By lowering slightly the blood-pressure it controls these phenomena.*

OXYTOCICS.

(Ergot, Hydrastis, Hydrastinine.)

Physiological Action.—*Ergot* in ordinary doses causes contraction of the uterus by augmenting the blood-supply of its walls*—a condition due primarily to the fact that it excites directly the vasomotor center. All the arteries of the body (with the exception of the arterioles, which are governed by the sympathetic center*) being constricted, the blood is driven into the smaller vessels and capillaries of all organs, including the uterine muscle. The contractile power of this muscle being

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* *Author's conclusion.*

[31] Lanphear: Kansas City Med. Index, Nov., 1898.

[32] Hallopeau and Vielliard: Ann. de derm. et de syph., 4 série, vol. v., p. 223, 1894.

proportionate, as in all organs, with the activity of its intrinsic metabolism, its sensitiveness to the reflex motor impulses which the uterus receives periodically during parturition is correspondingly enhanced.*

As stated by Manquat,[53] "it is generally admitted that ergot has a vasoconstrictor action upon the vessels; this opinion rests upon a large number of experiments." Holmes[54] observed the constriction of the arteries in the frog and in the albino rabbit, marked anæmia of the ears of this animal being noted. A rise of the general blood-pressure (preceded by a short period of depression) was also obtained experimentally by Köhler,[55] Eberty,[56] H. C. Wood,[57] Kobert and by Jacobi. Wood,[58] who refers to these experiments, states that "the rise in pressure, which is to be regarded as the characteristic effect of ergot upon the circulation, is due to a constriction of the blood-vessels," and that "Holmes, Wernich,[59] Vogt,[60] Kersch,[61] Schüller[62] and Briesemann[63] assert that they have seen invariably diminution in the caliber of the arteries under the influence of ergot."

The more recent experiments point in the same direction. Plumier[64] found that the intravenous injection of the fluid extract of ergot produces in the dog a marked elevation of the blood-pressure in the pulmonary artery. H. H. Dale[65] observed "a stimulant constrictor effect upon certain organs composed of plain or unstriated muscle-fibers, among which are the arteries, the uterus and the sphincter of the iris." The 300 painstaking experiments of Sollmann and Brown,[66] which seem to controvert all this evidence, are unfortunately of no value. They overlooked the fact that the anæsthetic they administered to their dogs, ether, caused a very marked rise of pressure, and that the ergot could not raise it beyond this level. Hence their erroneous conclusion that "there is no evidence of strong vasoconstriction." The slowing of the pulse is readily accounted for by the increased resistance of the blood-column to the cardiac contractions, produced by the general vasoconstriction.

That the rise of blood-pressure is due to a centric action was shown experimentally by J. C. Hemmeter,[67] who found that the rise did not occur when the spinal cord was severed, and, in accord with Wernich,[68] that after this operation ergot could no longer provoke uterine contractions.

Full therapeutic doses of ergot cause such marked constriction of the arteries that the lumen of the smaller vessels becomes sufficiently narrowed to interfere with the circulation.* The blood-stream being slowed in the arterioles and capillaries, the opposite condition to that described above is produced, viz., ischæmia of the organs which these small vessels supply.[*] The peripheral temperature is then reduced and the patient complains of cold—a danger signal which indicates that an excess of the drug is being administered.[*]

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* *Author's conclusion.*

[53] Manquat: *Loc. cit.*, vol. i, p. 71, 1903.

[54] Holmes: Thèse de Paris, 1870.

[55] Köhler: Virchow's Archiv, Bd. lx, S. 384, 1874.

[56] Eberty: Cited by Köhler: *Ibid.*

[57] H. C. Wood: Phila. Med. Times, vol. iv, p. 512, 1874.

[58] Wood: *Loc. cit.*, thirteenth edition, p. 746, 1906.

[59] Wernich: Virchow's Archiv, Bd. lvi, S. 505, 1872.

[60] Vogt: Berl. klin. Woch., Bd. ix, S. 115, 1872.

[61] Kersch: Betz's Memorabilien, Bd. xviii, S. 202, 1873.

[62] Schüller: Berl. klin. Woch., Bd. xi, S. 294, 305, 1874.

[63] Briesemann: Inaug.-Dissert., Rostock, 1869.

[64] Plumier: Jour. de physiol., vol. vii, p. 12, 1905.

[65] H. H. Dale: Jour. of Physiol., vol. xxxiv, May, 1906.

[66] Sollmann and Brown: Jour. Amer. Med. Assoc., July 22, 1905.

[67] J. C. Hemmeter: N. C. Med. Jour., Aug., 1891.

[68] Wernich: *Loc. cit.*

Before I had realized this fact, I caused complete—though temporary—inertia of the uterus by the use of excessive doses in a case requiring prompt delivery. I blamed the ergot at the time. Wood[99] states in the lower animals the symptoms of intoxication "are mainly paralytic, and that the only ones which are in any sense characteristic are the *anæsthesia* and the *coldness* of the surface. As this coldness of the surface has been noted in various women in whom the drug has caused fatal abortion, it is probably characteristic of the poisoning." Ringer and Sainsbury[100] found that ergotin slowed markedly the rate of flow through the arterioles. Hemmeter[101] noted that in poisoning the temperature sometimes fell more than 2° C. (3.6° F.) in human beings and 5° C. (9° F.) in animals.

Untoward Effects and Poisoning.—The earlier effects of ergot-poisoning are due to the great accumulation of blood in the peripheral vessels, which a large dose of the drug provokes by violently stimulating the vasomotor center,[*] viz., formication, tingling, giddiness, delirium, flushing, purpura, tinnitus, dilation of the pupil, colic, spasmodic contractions of the muscles, opisthotonos or emprosthotonos, and even epipleptic convulsions. The constriction of the vessels increasing rapidly, this hyperæmia is soon replaced by ischæmia[*] of the tissues: the skin then assumes an earthy hue, the surface becomes cold, there is great muscular weakness and fatigue, and numbness particularly of the extremities, nausea, vomiting, and the respiration is labored. More or less suddenly collapse occurs, due to hyperconstriction of the cardiac coronaries[*] and of the arteries of the anterior pituitary and thyroid.[*] The pulse then becomes very rapid and weak, the blood-pressure falls rapidly and death follows.

In *chronic ergotism,* which does not occur in this country, all these symptoms may develop gradually, but here another typical symptom of excessive constriction of the arteries occurs, viz., dry gangrene, beginning at one of the extremities, especially the toes, or the nose, lips and ear.

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[*] *Author's conclusion.*
[99] Wood: *Loc. cit.*, thirteenth edition, p. 747, 1906.
[100] Ringer and Sainsbury: Med.-Chir. Trans., vol. lxvii, p. 67, 1884.
[101] Hemmeter: *Loc. cit.*

The explanations submitted of these various symptoms are self-evident when the vasoconstrictor action of the drug is taken into account. Wood[illegible] states that "ergotic gangrene can readily be produced in the comb and tongue of chickens" and "von Recklinghausen asserts that the essential lesions in these cases are hyaline thrombi in the arterioles and capillaries"—an obvious proof that it is not these two kinds of vessels that are hyperconstricted, but the arteries behind them. Again, Wood states that "by toxic doses the rapidity of the heart's action is increased, and, according to Boreischa, galvanization of the par vagum has at this time little or no effect upon the pulse." The cause of this is also quite plain when interpreted from my viewpoint: the coronaries are already so constricted that stimulation of the vagi can contract no farther. Hence the cardiac arrest.

Therapeutics.—In the light of the above facts, a very small dose of ergot (10 minims of the fluid extract) is alone efficacious in the *uterine inertia* of parturition. Such a dose has also the advantage of avoiding tetanic contraction of the uterus, a condition which tends to cause retention of the placenta. Ergot is also useful in *post-partum hæmorrhage;* here a full dose may be given, and it may be administered hypodermically to obtain more rapid results. It has been used to prevent hæmorrhage from the lungs, stomach, intestines, etc., but the marked rise of blood-pressure it provokes before causing sufficient contraction to arrest the flow renders it a dangerous remedy in these conditions. In uterine hæmorrhage due to the presence of *fibroids* or other neoplasms, however, it has given excellent results, and tends to cause shrinking of the growth when given in full doses. In *chronic dysentery* and *chronic diarrhœa* ergot sometimes proves curative by causing hyperæmia of the small and large intestine and hastening resolution. It is of value also in *adynamic depression, melancholia* and neuropathies in which *hypochondria* is a prominent symptom, the benefit being due to the increased volume of blood which the cerebro-spinal system receives.*

DRUGS WHICH RESEMBLE ERGOT IN THEIR PHYSIOLOGICAL ACTION.

Hydrastis.—The physiological action of hydrastis and of its alkaloid hydrastine is similar to that of ergot. It stimulates the vasomotor center less violently, however, and its action in therapeutic doses is limited to the stage of hyperæmia of all organs, including the mucous membranes.* It has been used advantageously, therefore, in various disorders of the latter, viz., *chronic gastro-intestinal catarrh, chronic rhinitis, otorrhœa, dysmenorrhœa, chronic vaginitis, gonorrhœa*, etc.

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* *Author's conclusion.*

[illegible] Wood: *Loc. cit.*, thirteenth edition, p. 755, 1906.

Hydrastinine, an alkaloid obtained by the oxidation of hydrastine, has been employed with considerable success in uterine hæmorrhages, *menorrhagia*, and *metrorrhagia*, being more active than hydrastis or hydrastine as a vasoconstrictor. It is also useful in the same disorders as hydrastis, especially *dysmenorrhœa.*

DIURETICS.

The diuretics most used at the present time are drugs which have been treated in full in the preceding pages. Their property as such need alone be referred to.

Saline solution has been thought to act as an "hæmocathartic," the excrementitious products of tissue and other wastes, detritus, etc., being, it was believed, simply washed out of the blood by the excess of water introduced therein. I have shown in the earlier portion of this chapter that the process is really a nobler one, so to say, and that the introduction of saline solution into the organism enhances greatly the efficiency of the body's auto-protective processes. The proteolytic activity of the auto-antitoxin being greatly augmented,* there is soon thrown into the lymphatic channels an unusual quantity of products of catabolism which must be eliminated, partly by the urine. A prominent cause of diuresis is now present, viz., reflex stimulation of the secreto-motor center (located in the posterior pituitary) which governs renal action.* The kidneys are thus activated and a freer flow of urine follows—carrying along with it the excess of wastes. We need not inject a quart of saline solution to produce this effect; much smaller quantities will evoke it; but if at least a pint is employed the action will be greatly facilitated, since the organism promptly rids itself of the fluids that are useless to it. *Plain water* is an excellent diuretic for this reason, as is well known.

Digitalis.—When the infusion is used the fluid aids the process, and, as suggested by Huchard, it is probable that the mineral salts the leaves contain contribute somewhat to its diuretic effects. Diuresis may be obtained with digitalin, however, a fact which shows that the drug is itself active in this connection. Its mode of action becomes plain, in view of its main general property, that of a potent stimulant of the adrenal center.* As this stimulates metabolism in all tissues, we have again an unusual production of tissue-wastes and the same central excitation (reflex) of the renal functions that saline solution affords,* though caused in a different way. Of material aid to the process is the increased vascular tension which the drug causes by activating indirectly metabolism in the muscular coat of all arteries.* A rise of blood-pressure is a recognized cause of diuresis. Digitalis is especially efficient in cardiac dropsy—a result readily accounted for by the above-described physiological action.

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* *Author's conclusion.*

Squill acts much as does digitalis, including its action on the cardiac muscle, the arteries and general metabolism induced by a stimulating action on the adrenal center through the test-organ.* In large doses it stimulates the kidneys violently, causing sometimes hæmaturia. It is used in *dropsy, pleural* and *pericardial effusions* and the *cardiac dropsy,* but any form of nephritis is a contraindication to its use.

Calomel.—We have seen that this salt is an active diuretic also by enhancing general metabolism, thus causing rapidly an excess of waste-products in the blood.* When its use is prolonged it is also capable of causing grave renal disorders, including hæmorrhagic nephritis. It is very efficient in *cardiac dropsy,* however, and in *anuria* of asthenic origin in which the blood-pressure is low.

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* *Author's conclusion.*

CHAPTER XXIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS.

CANCER.

Time has also sustained views submitted nearly two decades ago in the present work. In the first edition (which appeared in January, 1903) I wrote:[1] "Certain growths, particularly the more malignant forms, sarcoma and carcinoma, seem closely connected with adrenal insufficiency and its normal consequences. We have seen that *trypsin,* fibrinogen [a nucleo-proteid compound] and the oxidizing substance were simultaneously necessary to insure the destruction of cells *in vitro,* and furthermore, that this process required, in addition, the presence of alkaline salts. That the destruction of worn-out or degenerated cells is a function of these very elements in the blood, is evident. Insufficiency of the adrenals, therefore, by reducing the relative proportion of these four constituents in the blood-stream, must correspondingly inhibit this physiological process in all parts of the organism." Thus, any region "may become the seat of this malignant growth, or rather of a local accumulation of the aberrant or worn-out cells which enter into its formation. The great vascularity of these growths suggests *an effort* of Nature to cause their elimination, but mitotic proliferation is alone induced, the blood being deficient in the four constituents which should insure destruction of the morbid cellular elements."

I pointed out also in this connection, in the same volume,[2] and under the caption "The Internal Secretions in their Relation to Immunity," that these "four constituents" were "the active immunizing agents of the organism," and that they owed their immunizing properties "to trypsin."

Over two years after I had done so, the close relationship between immunity and cancer was emphasized by several investigators: in this country by Gaylord, Clowes, and Baeslack;[3] in Germany by Ehrlich,[4] Schöne,[5] Sticker,[6] and others. The researches of the Imperial Cancer Research Fund investigators for 1906, 1907, and 1911[7] have shown, moreover, that a high degree of resistance to the transplantation of cancer in mice could be obtained. But curiously enough, this did not prevent the spontaneous development of cancer in these animals This from my viewpoint is due to the fact that the rôle of the endocrines in metabolism and immune chemistry has been persistently disregarded.

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[1] *Cf.* vol. i, p. 765, 1st Ed., 1903.
[2] *Cf.* vol. i, pp. 609 to 666 incl., 1st Ed., 1903.

Naamé, of Tunis[8] has recently reported cases of superficial epithelioma in aged subjects cured by organotherapy—thyroid gland and ovarian extracts in women and thyroid gland and testicular extracts in men. He attributed the disease to dysharmony between cell production and cytolysis, the indication being substances which promote growth—a need which the endocrines supply. As will be shown in the following pages both the factor and deficient defensive efficiency of the endocrines constituted the pathogenesis I have urged many years, with organotherapy, as salient indication—undoubtedly the lines will ultimately lead to mastery of this dread disease.

Definition.—Cancer is primarily due to hypoactivity of the body's auto-protective mechanism, the result, in turn, in a large proportion of cases, of premature senility. It is a vicarious over-growth of tissue-cells which the defensive agencies, leucocytic and humoral, should have destroyed in its incipiency, *i.e.*, when but a nidus of proliferating cells formed as a result of local irritation by traumatisms, inflammatory foci, parasites, moles, warts, etc. The defensive agents, phagocytes and auto-antitoxin, being those which, under normal conditions, carry on general nutrition, they are able only, owing to their insufficiency, to nourish the tumor and promote its development.*

This definition differs radically from those previously adduced by others, but the need of new lines of thought in this connection is emphasized by the labors of the Imperial Cancer Research Fund investigators, whose director, Dr. E. F. Bashford, wrote:[9] "In our investigations we have obtained evidence against all the explanations yet advanced as to the cause and nature of cancer," and, moreover, that "at present any attempts to directly ascertain the cause and nature of cancer are surrounded by so many sources of fallacy that," in his opinion, "they remain today as unprofitable as they have been in the past."

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* *Author's conclusion.*

[3] Gaylord, Clowes, and Baeslack: Med. News, Jan. 14, 1905; see also Clowes: Bull. Johns Hopkins Hosp., Apr., 1906.

[4] Ehrlich: Zeit. f. ärztl. Fortbildung, Bd. iii, S. 205, 1906.

[5] Schöne: Münch. med. Woch., Bd. liii, S. 2517, 1906.

[6] Sticker: *Ibid.*, Bd. liii, S. 1904, 1906.

[7] Bashford: Fourth Rep. of the Imperial Cancer Research Fund, 1911.

[8] Naamé: Gazette des Hôpitaux, No. 11. Feb. 5, 1921.

Symptoms.—The symptoms of cancer differ according to their location. The typical phenomena of the disease are in reality only witnessed when some external organ, the skin, the mammary gland, etc., is affected; while all the internal cancers soon provoke, in addition, morbid effects due to any interference with physiological functions which their presence entails. Common to all cases, however, is the terminal phase of the disease, *i.e.*, the cancerous cachexia, which consists of more or less rapid emaciation, anæmia and muscular weakness, the precursors of final exhaustion.

A brief survey of the leading symptoms can alone be given in this connection, and the reader is referred to special works for greater detail. In fact, the symptomatology would have been omitted were it not that the reader would have to consult works on dermatology, surgery, practice and special works on cancer to obtain even the present brief résumé of the various organs referred to. The division into "external" and "internal" cancers renders it impossible to illustrate the specific symptoms of the disease, those of cutaneous cancers, and, therefore, to differentiate them from those due to interference with functions.

EXTERNAL CANCERS.—*Skin.*—The starting point of *carcinoma* of the skin or mucous membrane may be an excrescence of long standing, such as a pigmented mole, an ordinary mole, a senile wart, or cutaneous disorders, a fissure or abraded area of the lip, a psoriatic or scaly sebaceous patch, an adenoma, a nodule, a scar, etc. Without apparent cause, but occasionally after irritation or injury, any of these apparently benign cellular aggregates begin to grow. They ulcerate at the base, mainly at the expense of the cutaneous structures, until finally the typical epitheliomatous ulcer is formed, *i.e.*, irregular in shape, with raised everted edges. The bottom of the ulcer is very uneven and covered with a fœtid sanious secretion, and bleeds readily when touched. It may assume various shapes; hence the "cauliflower" and other appearances. In most cases pain only comes on late, the discomfort being due to the ulceration.

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[9] E. F. Bashford: Brit. Med. Jour., Dec. 9, 1905.

When it appears it is of a lancinating character and may become very severe. The duration of cutaneous carcinoma varies greatly—from less than four years to decades. A favorite site is the lower lip; other regions frequently affected are the face, breast, genitalia, rectum, etc.

Cutaneous sarcoma is usually secondary, but it may develop primarily from a pigmented nævus or other cutaneous excrescence, especially when irritated. Sarcomata develop and multiply, break down and provoke metastases more rapidly than carcinomata, and death may occur within a few months, though in most cases life is prolonged a few years. The form that develops from nævi may retain its color, and merely grow and ulcerate, or it may become bluish or black, sessile, oval or spherical and hard; after growing for a while it ceases to do so, but others develop in other regions. All finally break down, forming melanotic ulcers which secrete a black substance and some pus. Death usually occurs from intestinal metastasis. Sarcoma may also appear as a diffused path or patches, beginning from minute brownish or purplish nodes, which become infiltrated and project, the skin being glossy and irregular. Various other rarer forms have been described, all embodying more or less prominently the characters just described.

Mammary Gland.—Two forms of cancer occur in this organ, the scirrhous, hard or fibrous cancer; and the encephaloid, or soft, cancer. In *scirrhous* cancer, the organ may preserve its form though becoming large and hard, the growth being deep-seated, or it may collapse or atrophy, the nipple being retracted, the so-called "withering" form. Again, a part of the breast alone may be affected, fibrous bands radiating through it and causing distortion of the organ. Conversely, it may be superficial at first, in patches or *plaques,* the skin appearing as though tanned, hard, rough and red. This may extend to the adjoining cutaneous tissues of the chest, the so-called "en cuirasse" cancer. The malignant growth may appear in the form of small, hard nodules of irregular size which may remain as they are if left alone, or ulcerate, and which promptly recur if removed. Ulceration may also occur when the growth is diffused, the ulcer resembling a crater with hard, everted edges, which bleeds easily and gives off a thin, offensive discharge.

The axillary glands are involved early, and as they enlarge may cause œdema of the arm or neuralgia by pressing upon the vessels and nerves. The entire lymphatic system is exposed to contamination; hence the visceral metastases often witnessed. After the tumor has reached a certain size, stinging, burning or neuralgic pains are complained of. As the ulcerative process advances, the toxæmia and cachexia do likewise, until the patient dies exhausted. *Encephaloid* cancer is not as frequently observed as the scirrhous form. It grows insidiously in the depth of the organ and finally reaches the skin. By gentle palpation, the tumor may be detected early in most instances; it may be fixed or movable, or nodular. At first, the skin is free, or traversed by prominent bluish veins, some of which may become varicose; red areas then appear—the precursors of adhesions with the cancerous mass. This soon becomes a fluctuating mass which ulcerates, becomes fungous, bleeds readily when touched, and gives off a foul odor. Cachexia appears earlier than in scirrhous cancer, and the burning, shooting pains and involvement of the lymphatics likewise. The softness of the growth predisposes it to hæmorrhages which are sometimes severe. Death occurs, as in scirrhous, from exhaustion.

INTERNAL CANCERS.—*Tongue.*—The anterior portion of this organ is the usual seat of cancer, which begins, as a rule, in a small fissure, ulcer or nodule on the side or edge, often where a sharp tooth, the stem of a pipe, a badly-fitting toothplate, etc., has for a time caused irritation. Psoriasis, scars, leucoma, cicatrices due to injury or syphilis, may likewise become the starting-point of a lingual epithelioma. When any one of these lesions becomes malignant, it soon assumes the aspect of a more or less deep and irregular ulcer with prominent edges, while the neighboring tissues, including often the floor of the mouth and gums, become infiltrated. Both the ulceration and infiltration may then extend posteriorly and involve the pillars of the fauces, the soft palate, the tonsils, etc. There is profuse salivation and the breath becomes extremely fœtid. The neighboring lymphatic glands become involved sooner or later, the prompt involvement denoting an unfavorable case. Gradually, deglutition and speech become difficult and starvation soon causes marked emaciation and weakness—a condition greatly aggravated when the ulceration invades arteries and causes hæmorrhages. After a year or two of intense suffering, death occurs from exhaustion.

Larynx.—Hoarseness, dyspnœa and cough and pain are early signs of cancer of the larynx. The pain is usually quite severe and lancinating, generally radiates toward the ear, and is sometimes especially marked during deglutition. Ulceration has usually begun when such is the case. Laryngoscopic examination often shows, at first, enlargement of one cord, then congestion of a restricted area which finally ulcerates. This becomes fungous and necrotic, and secretes a fœtid, sanious liquid which gives the breath and the sputa a foul odor. Ulceration of a large artery may cause profuse hæmorrhage, sufficient in some instances to compromise the patient's life; asphyxia by the entrance of food particles in the diseased larynx, and pneumonia from aspiration of detritus from the malignant mass, are additional dangers of cancer in this region. The general health is soon undermined owing to deficient nutrition, and the patient lapses into the cachectic state, dying of general marasmus.

Œsophagus.—Dysphagia, pain, and finally regurgitation of food and fluids are the characteristic symptoms of cancer in this region. As the morbid process advances the neighboring organs, the larynx, bronchi, pericardium, mediastinum, lymphatic glands, etc., may be involved either by ulceration or pressure, causing suffocation, bronchitis, inhalation pneumonia or other complications. Ulceration of the aorta or one of its branches may also occur and cause fatal hæmorrhage. As a rule, however, starvation, owing to the œsophageal obstruction, and exhaustion are the causes of death.

Stomach.—Pain in the epigastrium is present in practically all cases; but it is often preceded by a period of dyspepsia, sometimes attended with vomiting. In others the gastric disorders may be slight or absent, the main signs being those of pernicious anæmia, with intense pallor. Progressive emaciation is a constant feature of the disease, and is accompanied by more or less asthenia. When the cancer is situated near the cardia, spasm of the œsophagus and dysphagia may occur. Fever is present in about one-half of the cases, and may reach 104° F. (40° C.); in some cases the febrile process is continuous;

Glycosuria and indicanuria are commonly observed, peptonuria, sometimes. Death results occasionally from diabetic coma. Œdema of the ankles appears in the majority of cases and, in some instances, general anasarca supervenes. Hæmatemesis is observed in about one-fourth of the cases, the material vomited being always brown or black, the "coffee-ground" vomit. The tumor, when it has attained a certain size, can often be discerned both by inspection and palpation; the mass rises and descends during respiration—a sign especially marked in cancer of the pylorus.

Pancreas.—The earlier symptoms are gastro-intestinal, *i.e.*, indigestion and dull paroxysmal pain in the epigastrium, nausea, vomiting or diarrhœa, flatulence, the stools being greasy and clay-colored. Marked jaundice, due to obstruction of the bile-duct when the head of the pancreas is involved, ascites and diabetes are sometimes observed. In some cases a tumor may be felt in the pancreatic region, which differs from that of cancer of the gall-bladder, in that it is fixed. A distinct pulsation may be felt in the organ when the emaciation is sufficiently marked, owing to the fact that the growth lies directly upon the descending aorta. Prominent features of cancer of the pancreas are a rapid loss of strength and emaciation, soon followed by cachexia.

Liver.—Progressive enlargement of the organ, discernible on palpation, when sufficiently advanced, with pain and tenderness are the most common symptoms, especially if the growth is not far from the surface. Gastric disorders are frequently complained of. In about one-half of the cases, jaundice and ascites occur, accompanied in some instances by purpura, though the latter may appear in all cases, causing death frequently within three months.

Gall-bladder.—Cancer of this organ is almost always due to irritation by gall-stones. A firm, hard, irregular mass can often be detected at the site of the organ, which moves with the liver during deep respiration. There is more or less local tenderness on pressure, and severe paroxysmal—though sometimes continuous—pain. When the bile-ducts are involved, marked and persistent jaundice appears. The stools may be bloody and dropsy may occur, the latter being a feature of the cachetic stage.

Intestine.—The symptoms vary according to the position of the growth. Irregular attacks of acute colicky pains from two to five hours after a meal, according to the location of the tumor, nausea, vomiting, chronic constipation, with diarrhœa and meteorism, are almost always present, jaundice being superadded if the ducts of the gall-bladder are involved. When the intestinal obstruction is marked, the stools may assume a characteristic shape, *i.e.*, very small masses or lumps. The tumor may sometimes be detected by palpation through the abdominal walls, especially when the patient's muscles are relaxed by great weakness and when he has become greatly emaciated.

Peritoneum.—An uncomfortable sensation, with perhaps pain, in the abdomen followed by ascites, emaciation, and weakness are about all the symptoms observed at first. Differential diagnosis alone affords some clue to the nature of the disease: the age of the patient excludes tuberculosis of the peritoneum, which occurs in young subjects; the absence of fremitus distinguishes it from echinococcic cysts, another disorder which it greatly resembles. The neighboring organs, including the uterus, ovaries and rectum, should be examined in view of the fact that cancer of the peritoneum is often secondary. The inguinal glands are often enlarged. The tumor is discerned with difficulty owing to the ascites, but it can usually be felt after paracentesis. The vessels of the malignant mass sometimes rupture, causing severe hæmorrhage and aggravating the cachexia.

Uterus.—If the growth begins while the woman is still menstruating, intermenstrual spotting and a serous discharge are likely to appear. The presence of such signs after menopause is also significant. The slight discharges gradually become more frequent and abundant, and finally emit an unpleasant odor, the fœtor becoming very marked when necrotic tissue is present. Pain does not occur until the morbid process is well advanced, and is due to involvement of the neighboring tissues and their nerves; at first it is apt to radiate into the iliac region and hip, but involvement of the bladder, rectum and peritoneum gives rise to the characteristic pains that attend inflammation of these organs. Examination of the uterus should be practiced as soon as possible, to confirm the suspicions awakened by the general phenomena. Intense anæmia, general weakness, and the symptoms of the cachectic period finally appear, though death is often due to uræmia.

Rectum.—Uneasiness in the sacral region and along the inner side of the thighs, which after prolonged exertion may become actual pain radiating towards the rectum, are usually the earliest symptoms complained of. Morning diarrhœa, the discharge being watery, differing as to odor from the usual liquids voided, and often tinged with blood, is then observed, though this be interrupted by periods of constipation. When the stools are formed, they may be ribbon-like when the growth is low down. Local pain, which occurs late and is severe, especially during defecation, if the growth is near the anus, eventually becomes continuous. Hæmorrhages may then appear and become more frequent when ulceration occurs, thus aggravating what general debility may be present. The lymphatic glands of the region, pelvic and lumbar, are often enlarged and the liver also in some instances. The body gradually wastes and finally lapses into the characteristic cachetic state.

Pathogenesis and Pathology.—Advanced age is the predominating predisposing cause of cancer, but since the disease does not occur in all aged individuals, an additional predisposing factor is necessary. This factor may be said to include all morbid influences, inherited or acquired, which tend further to debilitate the organism. Although cancer is witnessed among the poor and ill-fed, and its development may follow exhausting toil, great anxiety, prolonged illness and other debilitating conditions, it occurs at least as frequently among subjects who have not been exposed to similar untoward influences, *i.e.*, the well-to-do and well-fed, and even the over-fed. In all these, however, inherited vulnerability to disease, which means inadequate activity of the auto-protective mechanism—the adrenal system—may none the less be present, and when advanced age is reached, the organism is unusually vulnerable to disease among the rich and poor alike.* In the over-fed, the wear and tear imposed upon the digestive apparatus, the excessive stimulation of the

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* *Author's conclusion.*

organs which supply the digestive ferments, and the overloading of the lymph and blood with more or less perfectly catabolized waste-products, gradually undermine all physiological functions, thus affording the accessory factor which with senility predisposes any part of the body, any organ, to the development of cancer.[*]

Bashford,[10] alluding to results reached in the Imperial Cancer Research Fund laboratories, states that "the association of cancer with old age is the only factor known to be constantly associated and intimately bound up with the processes responsible for the development of cancer in man and animals." He also calls attention to the fact that "cancer has the further remarkable common feature that in animals it has the same higher incidence in old age, and therefore the same relation to the duration of life as in man." Freund,[11] after a comprehensive study of the etiology of cancer, concludes that senilism is the primary etiological factor, but moreover, that it could be premature and even localized as well as generalized. This accounts for the occurrence of cancer at times in younger subjects—a fact which the British Research Commission has also elucidated recently, its labors having shown, according to Sir William Church,[12] that cancer in the young occurs for the most part "in tissues and organs which lose their functional activity in early life, and normally undergo degeneration and more or less absorption."

The presence of an additional predisposing cause is shown by the relationship of cancer with tuberculosis—first pointed out by Krauss, in 1832. Thus, Roger Williams[13] states that "no hereditary condition is more favorable to the development of cancer than that which predisposes to and accompanies tubercle." Moak[14] reported five cases in which carcinoma and tuberculosis were present in the same organ. H. R. Jones[15] found that in England and Wales, a high percentage of phthisical persons had a cancerous family history, and the age period at which the mortality of tuberculosis reached its zenith, 35 to 45 years, coincided with the period at which the cancer death-rate began to increase. In Ireland[16] a collective investigation by the registrar-general showed that in many cases cancer occurs in the same family; grandparents, parents and other relatives, and that the family likewise shows a predisposition to tuberculosis. Closely related to this feature of the problem is the observation of Roger Williams,[17] that in multicellular animals and plants, tumors rarely occur when these organisms live in a state of Nature, and that they are met with almost exclusively among domesticated varieties, especially those that have been kept long in confinement.

In a careful analytical study of the twelfth United States census, Guthrie McConnell[18] found, moreover, that those employed in hard outdoor work showed a higher cancer mortality than those of sedentary habits, while Freund[19] witnessed a number of examples in which a chronic, though mild, gastric disorder became a rapidly fatal cancer after excessive worry or overwork. Finally, Jonathan Hutchinson[30] refers to twelve cases of cancer which had developed in subjects who had been long under the influence of arsenic, and ascribes the tendency of chimney-sweeps to the large proportion of arsenic in certain coals. We have seen that arsenic is the physiological antagonist of thyroid extract, and that it depresses the functional activity of the adrenal system and, therefore, that of all vital processes. Robert Bell[31] writes: "That the thyroid has an important relationship to the incidence of cancer is borne out by the fact that in cancer subjects it is invariably found to be more or less atrophied, hence it is necessary to supplement the modified dietetic measures recommended, by the administration of either thyroid gland substance or its active principles. By these means we have reason to hope the gland may recover its lost power and thus be enabled to resume its physiological activity, which is quite within the range of possibility."

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[*] *Author's conclusion.*
[10] Bashford: *Ibid.*
[11] Freund: Zeit. f. Krebsforschung, Bd. iii, S. 1, 1905.
[12] Sir William Church: Lancet, July 8, 1905.
[13] Roger Williams: "Diseases of the Breast, etc.," London, 1894.
[14] Moak: Jour. of Med. Research, June, 1902.
[15] H. R. Jones: Lancet, Nov. 12, 1904.
[16] Jour. Amer. Med. Assoc., Apr. 18, 1903.
[17] Roger Williams: Brit. Med. Jour., July 30, 1904.
[18] Guthrie McConnell: Jour. Amer. Med. Assoc., Apr. 28, 1906.
[19] Freund: *Loc. cit.*

The predisposing influence of over-eating is emphasized by the importance attached to the gouty diathesis, long ago, by French clinicians, Bazin, Bouchard[32] and others, and more recently by Felix and Robert Bell[33] and Vigouroux.[34] Rabagliati,[35] Roger Williams[36] and Chittenden,[37] likewise incriminate excess of nutritive material in general. That the predisposition to cancer is a *result* of the excessive ingestion of food is shown by the fact that the age incidence of cancer succeeds that of gout. Indeed, as stated by Bazin, "the gouty *end up* especially with cancer, particularly by cancer of the rectum and bladder." It is an expression, in these cases, of the chronic phase of gout, which phase, as stated by Levison,[38] is attended by debility of the patient, and may also "appear in feeble subjects as the only manifestation of gout."

Still, if we are dealing with *general* adynamia, why is the cancerous growth localized?

A cancer develops from a preëxisting aggregate of adventitious cells,* whether the latter constitute a mole, a nævus, a wart, a fibroma, etc., or patches of eczema, psoriasis, paraffin acne, cicatricial tissue, etc., or an ulcer, fistula or other lesion of the skin or mucous membranes, or whether it occur as a result of localized and chronic inflammation in the deeper or internal organs. As long as the nutrition of any one of these local cell-aggregates is adequately controlled by its arterial blood, it retains its benign character;* when, however, a debilitated condition of the organism, such as that brought about by senility or any of the other predisposing conditions just reviewed prevails, it develops a malignant growth. The morbid process which entails this result is as follows: the vascular centers, vasomotor and sympathetic, along with the rest of the organism, become functionally depressed; as this causes relaxation of all arteries, including the cutaneous arterioles, the adventitious cell-aggregate receives an excess of blood (a process encouraged by the reflex influence of the sensory terminals it contains and which multiply with the tumor), and if the passive hyperæmia or congestion is sufficiently marked, it begins to grow, if already a defined tumor, or it assumes the characters of a tumor if merely a patch of abnormal cells.* In the case of moles, nævi, warts and other superficial conditions, traumatisms, *i.e.*, scratching, friction of clothing, blows, etc., are sufficient to initiate such a process in the same class of subjects, by greatly aggravating a local hyperæmia which might not otherwise have become sufficiently active to provoke development into a malignant tumor.*

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* *Author's conclusion.*

[30] Jonathan Hutchinson: Deut. med. Woch., Bd. xxx, S. 1378, 1904.

[31] Robert Bell: Med. Record, Feb. 16, 1907.

[32] Bouchard: "Mal. par ralent. de la nutrition," second edition, 1885.

[33] Robert Bell: Med. Record, Aug. 15, 1903.

[34] Vigouroux: Revue de thérap., Sept. 1, 1906.

[35] Rabagliati: "Air, Food and Exercise," London, 1897.

[36] Roger Williams: Edinburgh Med. Jour., Nov., 1897.

[37] Chittenden: Amer. Medicine, Nov. 11, 1905.

[38] Levison: Sajous's "Analyt. Cyclo. of Pract. Med.," Art. "Gout," edition 1903.

The importance attached by many clinicians in recent years, as shown by the papers of Eve,[29] Wilson and Kalteyer,[30] Bloodgood,[31] Keen[32] and others, to the removal of warts, moles, pigmented nævi and kindred cutaneous excrescences lest they become malignant, harmonizes with these conclusions. Indeed, Eve found that out of 33 cases of melanosarcoma, 78 per cent. began in pigmented moles, while Wilson and Kalteyer found that out of 51 cases of cancer collected by them, 69 per cent. had their origin in a mole or nævus. Moreover, the well-known corresponding effects of prolonged irritation of limited areas by broken teeth, the pipe, scars, paraffin acne, lingual psoriasis, etc., sufficiently emphasize the pathogenic influence of localized processes. Bergmann,[33] in fact, asserts that carcinoma of the extremities does not occur without some cutaneous lesion, scar, fistula, ulcer, eczema, wart or mole as a precursor. Suggestive in this connection is the observation of Leo Loeb,[34] that in cattle the most frequent place for the occurrence of carcinoma is the inner canthus of the eye—a region greatly exposed to irritation and injury by twigs, strawtips and the like, while such animals are feeding. In an extensive study of cancer in the domestic animals, Sticker[35] found that in the horse the nose was commonly diseased, an organ considerably exposed to scratches and other traumatisms in the manger.

This applies likewise, in a certain sense, to cancer of the stomach, intestines, rectum, kidneys, bladder, gall-bladder and uterus. All these organs are exposed to the chemical and physical action of any abnormal constituent present in the substances passed through them—products of imperfect digestion in the alimentary canal, toxic wastes in the hepatic and urinary systems and in the uterine discharges, etc. Maniscalco,[36] by repeated chemical and mechanical irritation of the exposed gastric mucosa of dogs, caused growths which presented all the features of cancer. Bazin observed, as stated, that cancer of the bladder and rectum *followed* gout; the prolonged excretion of poisonous waste-products obviously stands here as local irritant. This affords also an example of the manner in which chemical substances in the blood, secretions and excretions, can predispose a restricted territory of tissue-cells to cancer, by provoking therein the proliferation of new cells, atypical in the sense that, as inflammatory products, they are adventitious, and therefore, like warts, moles, and the like, menacing excrescences.

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* *Author's conclusion.*

[29] Eve: Practitioner, Feb., 1903.

[30] Wilson and Kalteyer: Amer. Jour. Med. Sci., Nov., 1903.

[31] Bloodgood: "Progressive Medicine," p. 264, Dec., 1903.

[32] Keen: Jour. Amer. Med. Assoc., July 9, 1904.

[33] Bergmann: Berl. klin. Woch., Bd. xlii, S. 232, 1905.

[34] Leo Loeb: Medicine, Apr., 1900.

[35] Sticker: Arch. f. klin. Chir., Bd. lxv, S. 1023, 1902.

[36] Maniscalco: Riforma medica, vol. xxi, p. 340, 1905.

The functional relationship between the abnormal cell-aggregates and the nervous system is readily demonstrable even in such apparently functionless structures as a mole, a nævus, and the like, so prone, as stated above, to become malignant. Wilfred S. Fox,[37] in an exhaustive paper, remarks that "this connection between moles and the cutaneous nerve-supply is not surprising when one considers the intimate developmental relation between the skin and the nervous system." Foldau[38] traced nerve-fibers in these structures, while Bergmann[39] states that multiple pigmented nævi also contain nerve terminals. That they persist in cancerous neoplasms is shown by the fact that H. H. Young,[40] using Ehrlich's methylene-blue method in ten freshly removed carcinomata and sarcomata, found distinct axis-cylinders sometimes in considerable numbers, in no less than five growths, *i.e.*, cancers of the breast, cervix and tibia.

As to the rôle of the vasomotor nerves—which govern nutrition—G. Lenthal Cheatle[41] pointed out that a proportion of cases of cancer showed a "marked relationship between the spread of the primary focus and the distribution of nerves and *trophic* areas" and adduced a large number of cases, convincingly illustrating the close relationship between the initial lesion of cancer (frequently a mole) and points at which nerves become cutaneous, including the maximum pain points of Head.[42] Although most of the cases related are not—in the light of my views—truly cancerous (being instances of rodent ulcer due to *deficient* nutrition of the cutaneous elements, and not of *growths* due to *over*nutrition of these elements) the fact remains that they clearly sustain Cheatle's opinion that trophic nerves are concerned in the morbid process.

The influence of senility, the uric acid diathesis and other predisposing conditions have already been reviewed. That this should entail depression of the vascular nerve-centers, and, therefore, general vasodilation and passive congestion of any moles or other excrescences present, is self-evident. The effects of injury on these small growths are now thoroughly recognized. Thus W. W. Keen[43] writes that "all such growths are exposed to traumatism, such as blows, friction of the clothing, scratching on account of the itching, or in many cases on account of the presence of a little scab—and who can and does resist the temptation to scratch off these scabs?" . . . . "In consequence of such injury or repeated and long-continued irritation—or in other cases without any assignable cause—they begin to increase in size. This sudden activity and increase in size usually does not occur for months or more likely years; it may be thirty or fifty years, or even more, after the mole or wart was first noticed. The moment they begin to increase in size, they are, I believe, almost invariably malignant growths."

All this (apart from the traumatisms, which probably act as exciting causes of cancer of the breast and bones) is as applicable to the pathogenesis of internal cancers, the passive vasomotor hyperæmia being sufficient here to start the process of growth in a restricted area, the uterine os, for instance, which has become the seat of a local predisposing disorder, a chronic catarrhal process, cicatricial tissue incident upon parturition, etc., any condition, in fact, involving localized cell proliferation.

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[37] Wilfred S. Fox: Brit. Jour. of Dermat., Jan., 1906.
[38] Foldau: Cited by Cheatle: Brit. Med. Jour., Apr. 18, 1903.
[39] Bergmann: *Loc. cit.*
[40] H. H. Young: Jour. of Exper. Med., Jan., 1897.
[41] G. Lenthal Cheatle: Brit. Med. Jour., Apr. 18 and Dec. 12, 1903.
[42] Head: Brain, vol. xvi, p. 1, 1893; vol. xvii, p. 339, 1894.
[43] W. W. Keen: *Loc. cit.*

At first, the process of growth is localized, in the sense that the body at large does not participate in it. When, however, the tumor has reached a certain size, its presence becomes a menace. Its structure differing from that of normal tissues in that the channels for the elimination of broken-down cells, waste-products, etc., are either absent or very imperfect, it becomes, in respect to the body at large, a source of auto-intoxication. This evokes a general febrile reaction similar, in a measure, to that provoked by a subcutaneous abscess. The adrenal system being stimulated, the blood soon becomes supplied with an excess of auto-antitoxin, the constituents of which permeate the growth as they do all other organs during fever.*

The development of the tumor is thus intimately merged with the immunizing process.* There is excessive oxygenization, owing to the overproduction of adrenoxidase and, therefore, of trypsin and nucleo-proteid.* There is also an abundant leucocytosis, the cells serving not only to supply the fluids of the growth, the trypsin and the nucleo-proteid found in it, but also to insure active phagocytosis.*

The general reaction is sufficient in some cases to provoke fever—which occurs only when the adrenal system is violently stimulated. Fretel[44] observed a rise of temperature in the absence of any complication, especially in cancers of rapid evolution. Freudweiler,[45] at the instigation of Eichhorst, studied the clinical histories of 475 cases of carcinoma, and found that the temperature exceeded 38° C. (100° F.) in no less than 117, although all cases in which some complication existed were excluded. Even the central phenomena of a febrile process are present. De Buck and Van der Linden[46] found the tendon reflex invariably exaggerated, while Klippel[47] noted a marked hyperexcitability of the muscles, contraction being produced very readily by percussion.

The three constituents of the "functional triad" which constitute the active agencies of the febrile process, *i.e.*, the auto-antitoxin, have been found in the growths themselves, thus proving that they take part in this process.

The presence of *adrenoxidase* in these growths is shown by the characteristic tests. Thus, Hugounenq and Paviot,[48] in soft malignant tumors, not only obtained the typical guaiac reaction, but also the intense violet of the paraphenylene-diamine test. Moreover, boiling of the cancer fragment destroyed this specific property, which was not marked where the process of growth was most active. They characterize as "oxidizing diastase" the "soluble ferment" to which they ascribe these results, and compare the latter to those of Bertrand and Bourquelot, referred to in the thirteenth chapter of this work. The presence of *trypsin* in cancerous growths is no less evident. Stewart[49] found a high percentage of trypsin in secondary growth of the liver and lung in a case of pancreatic cancer. This suggests direct metastasis, but we have seen that trypsin is present in all cells, as shown by the researches of Hedin, Cohnheim, Opie and others. Blumenthal,[50] moreover, found a corresponding enzyme in cancer cells, not specific to cancer cells alone, but capable of attacking all tissues. The third constituent, the *nucleo-proteid*, is likewise present in all tissues, as already shown. That leucocytes (which secrete this substance in the form of granules) are present in large numbers, is well known. Thus, Herbert Snow[51] pointed out twelve years ago that every variety of malignant growth exhibits from its earliest initiation, an extremely copious immigration of leucocytes, which steadily increases. Bushnell[52] found that this sometimes reached as high as 32,580. Snow noted, however, that this *leucocytosis* was restricted to the normal tissues immediately bordering the cancerous parenchyma. This has been confirmed by many observers, and recently by Farmer, Moore and Walker.[53] Even the specific (oxyphile) granules themselves have been found in the tumors by Ehrlich, Löwit and Przewoski,[54] although these investigators were not aware of their functions. The granules took acid aniline dyes readily, did not become black under osmic acid, etc., the characteristic tests. They were of course observed in *extra* corpus specimens, and therefore under abnormal conditions. During life, however, they dissolve in the blood, and, with the adrenoxidase and trypsin, form the "digestive triad" or auto-antitoxin, distributed throughout the growth itself.

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* *Author's conclusion.*

[44] Fretel: Thèse de Paris, 1899.

[45] Freudweiler: Deut. Arch. f. klin. Med., Bd. lxiv, S. 544, 1899.

[46] De Buck and Van der Linden: Presse méd., vol. x, p. 10, 1902.

[47] Klippel: Arch. gén. de méd., vol. clxxxiii, p. 33, 1899.

[48] Hugounenq and Paviot: Lyon médical, vol. lxxxii, p. 1, 1896.

The tumor is supplied with the elements for its development, *i.e.*, the nucleo-proteids out of which its tissues are nourished by the leucocytes.* These cells, as previously shown, ingest food-products and enterokinase—which contains trypsin—in the intestinal canal and convert them into granulations which they carry to the lymphatic spaces and deal out to the tissue-cells.* The chromatin of the latter, which undergoes atypical mitosis and other transformations, was also shown to be derived from the leucocytic granulations.*

Bashford,[55] referring to various hypotheses upon the mode of origin and nature of cancer, states that "they fail to show how the actual cell multiplication is maintained." In truth, it is upon this point that they have all collapsed.

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* *Author's conclusion.*

[49] Cited by Morris: Review of Reviews, Dec. 25, 1903.

[50] Cited by Von Leyden: "Ueber die parasitäre Theorie in der Ætiologie der Krebs.," Berlin, 1905.

[51] Herbert Snow: Brit. Med. Jour., Sept. 22, 1894.

[52] Bushnell: *Ibid.*, Sept. 12, 1903.

[53] Farmer, Moore and Walker: *Ibid.*, Aug. 12, 1905.

[54] Przewoski: Centralbl. f. allg. Pathol. u. path. Anat., Mar. 15, 1896.

[55] Bashford: Lancet, Apr. 1, 1905.

French investigators long ago observed that the leucocytes exerted a fructifying influence upon cancer cells, causing them to multiply.[56] The manner in which they do so, however, has never been explained. The direct participation of the leucocytes outlined in the text affords this explanation. Indeed, as I have pointed out, these cells are the actual builders of living tissue. This implies that the mitotic figures observed in cancerous masses, and now regarded as reproductive cells, are really nothing but those common to ordinary cells, including leucocytes. Bashford wrote recently:[57] "During the past year a paper has been communicated to the Royal Society, showing that the nuclear figures in cancer cells, believed to indicate the occurrence of a true 'reducing division,' are in reality of the ordinary type. Dr. Murray and myself have invariably denied that the presence of cell-divisions resembling those of reproductive tissue were a means of distinguishing benign from malignant new growths."

This accounts for another paradoxical fact emphasized by the Royal Cancer Research Fund investigators, namely, that, as stated by Bashford,[58] "the influence of age is active in relation to the *origin* of cancerous growth, and not in relation to its *continuation;* for cancer can be propagated almost better in young than in old animals." As I have stated, age stands merely as a predisposing factor, while the general vasodilation which it engenders and the febrile process, by flooding the tumor with nutritional elements, are the causes underlying its growth. As young animals are better able to promote a vigorous febrile reaction than old ones, the process of growth is all the more active.

Again, "malignancy," if these processes actually prevail, should merely mean excessive tissue-growth. The labors of the Royal Cancer Research investigators also sustain this conclusion. Bashford[59] remarks in this connection: "What is understood by the malignancy of a tumor is but a manifestation of the power of growth: a conclusion to which Ehrlich and Apolant have recently given confirmation." The Cancer Research Commission also confirmed Jensen's conclusion that the growth of artificially propagated cancer was due to the continued proliferation of the parenchyma cells—a logical outcome, I may add, with the leucocytes as the normal purveyors of nutriment to the normal parenchyma.

There are, of course, several varieties of carcinoma: (1) *epithelioma,* consisting of surface epithelium, which includes two kinds: the *squamous* of the skin and mucous membrane of the lips, œsophagus, and cervix uteri, etc.; and the *cylindrical* or columnar of the gastric, intestinal and uterine mucous membranes; (2) the *granular,* consisting of acini or alveoli in layers—and which may become fibrous, the scirrhous form—and growing mainly in the pylorus, mammary gland, pancreas, kidneys, ovaries and testicles; (3) *colloid* or gelatinous, consisting of transparent, jelly-like masses, containing degenerated tissues and epithelial cells, and met with in the ovaries, stomach, intestine, peritoneum, and mammary gland; and (4) *deciduoma*

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[56] Warren: "Surgical Pathology and Therap.," vol. ii, p. 642, 1895.
[57] Bashford: Brit. Med. Jour., July 26, 1904.
[58] Bashford: *Ibid.*, Dec. 9, 1905.
[59] Bashford: *Ibid.*

malignum of the placenta, consisting of fœtal epithelial cells (syncytium) and of different cells of the chorion villi.

Several varieties of sarcoma are also described: (1) *spindle-celled sarcoma*, which occurs in the connective tissue of bones, tendons, fasciæ, and occasionally in the soft tissues; (2) *round-celled sarcoma*, often permeated with large blood-vessels, and more malignant than the former, is itself divided into two varieties: *lymphosarcoma*, which occurs in the lymphatic glands and the lymphadenoid tissues of mucous membranes, and *alveolar sarcoma*, which contains also spindle-cells, acini filled with large, round cells and fibrous tissue, and is notable because it commonly develops from cutaneous moles, nævi and warts, and from lymphatic glands and serous membranes; (3) *angiosarcoma* (a very malignant growth), which starts in the external coat or adventitia of blood-vessels, is usually very vascular—thus exposing them to rupture and provoking hæmorrhage—likewise grows, as a rule, on the skin and particularly from pigmented warts and moles, and also in the eye and the pia-mater; (4) *giant-celled sarcoma*, a relatively benign growth, which usually occurs in bone or bone-marrow (hence often called osteo- or myelo-sarcoma), the large multinuclear cells of which resemble the myelo-plaques of bone.

The difference between all these varieties depends upon the histological composition of the structures which form the tumor. At first, all the tissues composing the affected area are involved in the hypertrophic process; eventually, however, the epithelium in carcinoma or the connective tissue in sarcoma grows with greater rapidity than all the other local structures and soon constitutes the bulk of the tumor. The development of sarcoma coincides, however, with the maximum energy developed, *i.e.*, with the most active local accumulation of nutrient leucocytes and of the energizing agents, adrenoxidase and nuclein, which this phenomenon entails.*

All the various varieties of cancer enumerated are ascribable to the same cause: a primary focus of proliferation-cells due to local (active or passive) irritation, which eventually provokes marked local congestion and excessive nutrition.* Important in this connection, however, is the fact that this local hyperæmia and accumulation of all the constituents of the blood which usually provoke inflammation do not initiate the latter in cancerous growths.* The local congestion, leucocytosis, etc., are associated with a process distinct from that of inflammation though linked with it, *i.e.*, the process of tissue repair.* Were it otherwise, the tumor would not grow; it would be destroyed, and as will be shown, it is by provoking active inflammation in the growth itself that cancer can be mastered.*

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* *Author's conclusion.*

Many investigators, including Israel,[60] now ascribe to relative overactivity, the proliferation of epithelial cells over all others, with persistent excitation as a primary cause. Even in the giant-celled sarcoma, though situated in osseous tissues, this exciting cause prevails. Ziegler maintains, writes Stengel,[61] referring to this variety of growth, "that the presence of giant-cells does not form an essential characteristic of a peculiar type of tumor, but that it is accidental, resulting from *continued irritation*." The result of this irritation also manifests itself by overnutrition in sarcoma. Thus, H. W. Cattell[62] states that "it is at times impossible from microscopical study alone to tell a sarcoma from *granulating tissue*."

It is now generally conceded that at first all the elements of the tissue involved are more or less urged to grow as shown by Schuchardt.[63] In the early stage of cutaneous epithelioma, he observed that "not merely the epithelium, but all the tissues of the skin, the connective tissue as well, show hypertrophic changes," though "later, the overgrowth of epithelial cells outruns and overshadows that of the other tissues."

That sarcoma, in which the connective tissue predominates, is but an advanced stage of the carcinomatous stage, was recently observed by Apolant and Ehrlich,[64] in the course of inoculation experiments in mice. The carcinomatous type was traced up to the sixth generation. By the tenth a change had occurred: the tumor was a mixed one, a sarcomatous stroma predominating. By the fourteenth, no carcinomatous tissue remained. They refer to a similar transition in man, observed by Schmorl, a case of epithelioma of the thyroid. After removal, the tumor, which recurred locally, was a mixed carcinoma and sarcoma. A second removal being followed by death from metastasis, all the growths examined were found to be pure spindle-celled sarcomata. Hansemann[65] has encountered carcinomata with sarcomatous stroma, and refers to twenty cases in literature. Apolant and Ehrlich did not always obtain such prompt transitions, however. In some instances the mixed growth was only reached in the sixty-eighth generation; then followed a violent reaction, during which the tumor became a pure sarcoma. So great was this "energy of growth" that in the course of a few weeks, in some instances, the tumor was larger than the mouse itself. They state that at the present time no explanation is available for this phenomenon, though they suggest that the development may be due "to chemical changes in the carcinoma cells and gradual stimulation of the connective tissue cells." What better and more solidly grounded explanation can there be vouchsafed than one of which *all* the elements of growth are actually present in the tumor, as we have seen, and which *alone* can account for the violent "energy of growth" to which they refer? We are thus brought to consider overnutrition as the underlying cause of *all* types of malignant growths.

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* *Author's conclusion.*

[60] Israel: Archiv f. klin. Chir., Bd. lxvii, S. 446, 1902.

[61] Stengel: "T. B. of Pathol.," third edition, p. 154, 1900.

[62] H. W. Cattell: Sajous's "Analyt. Cyclo. of Pract. Med.," Art. "Tumors," vol. vi, 1901.

[63] Schuchardt: Archiv f. klin. Chir., Bd. xliii, S. 255, 1892.

[64] Apolant and Ehrlich: Berl. klin. Wochen., Bd. xliii, S. 871, 1906.

[65] Hansemann: Zeit. f. Krebsforschung, Bd. i, S. 183, 1904.

All malignant tumors being the outcome of a localized overdevelopment of cells initiated by irritation of the area involved, any agent capable of provoking the appropriate type of irritation can cause a cancer. As various parasites, including bacteria, have, in the hands of the upholders of the parasitic theory, provoked the formation, local and remote, of cancerous growths, there may be classes among these appropriate irritants.* Moreover, as the growths developed through inoculations and implantations present the morphological organization of sporadic cancers, those provoked by the upholders of parasitic theories are true cancers.* It cannot be said, however, that cancer is a parasitic disease, since all malignant growths can be caused by various factors, intrinsic and extrinsic, which irritate the tissues, irrespective of any parasite.*

The multiplicity of these factors also accounts for the epidemics of cancer, its repeated occurrence in certain houses or districts, and for the cases of direct contamination on record, since the presence of any of the appropriate irritants in these houses or districts or on the contaminating surface, whether this be normal or the seat of malignant growth (both fragments and fluids therefrom being effective inoculative agents), is sufficient to start a malignant process in predisposed tissues.* A tissue being predisposed to malignancy when it is the seat of adventitious cells in an aged or debilitated subject, an ulcerated surface, however small, on the lips, tongue, œsophagus, uterus, etc., may become a vulnerable spot if it happens to become inoculated when any one of the cancerogenic factors happens to become implanted therein.*

Merged in with the tissues of the tumor and imprisoned among them are cells which have been taken by many investigators as the specific cause of cancer. Cornil,[80] Fabre Domergue and others have shown that the many cellular and nuclear elements present could readily be taken for parasites. The nuclei, which are rich in chromatin, soon become fimbriated, knobbed, sometimes œdematous, and finally achromatic, assuming at the same time most varied shapes and appearances.

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* *Author's conclusion.*

[80] Cornil: Boston Med. and Surg. Jour., Apr. 19, 1894.

Councilman[67] also found that parasites to which specific properties had been attributed, were present in many morbid processes other than cancer. In accord with this observation, Borrel[68] pointed out that the sporozoa associated with tissue-proliferation in sheep-rot, variola, bovine pest and other diseases, corresponded with the detritus of worn-out leucocytes. Borrmann[69] recently showed, moreover, that none of the so-called parasites are found in very small, young cancers, thus eliminating them as a cause. Transplantation experiments are as conclusive. Jensen,[70] for instance, made transplantations in 844 mice and obtained successful results in about 50 per cent. Although cell inclusions were undoubtedly present and the tumors grew until the mice died of cachexia, he never observed parasites, and experimental inoculation invariably gave negative results. This has been confirmed, according to Bashford,[71] in the Royal Research laboratories, where at least 50,000 transplantation experiments were performed. Referring to researches conducted under the same auspices, Sir William Church[72] states that "large numbers of healthy mice have been kept for long periods in the same cages with mice suffering from both sporadic and inoculated tumors," and that "in no single instance did the malignant growth occur in an inoculated mouse." As emphasized by Leo Loeb,[73] though he had carried on highly successful experimental inoculations, inoculability does not mean infectivity. On the whole, as stated by Senn[74] at the recent Lisbon Congress, in reference to the specificity of microbes and other parasites in cancer: "Searching criticisms from different reliable sources have disarmed all such claims."

Nevertheless, the fact remains that many investigators, beginning with Morau, in 1885, *i.e.*, Sanfelice,[75] Roswell Park,[76] Gaylord,[77] Doyen,[78] Sticker,[79] Vischer,[80] Schmidt,[81] and many others, have obtained by inoculation growths resembling cancers to such a degree that microscopical examination was necessary to determine their identity. In the light of my views, as defined above, the reports of the opponents of the parasitic theory indicate that these growths were true cancers. "By the investigators themselves," writes Lazarus-Barlow,[82] "they have been regarded as 'epithelial,' 'malignant,' etc., but by opponents of the parasitic theory they are confidently asserted to be 'infective granulomata,' that is, inflammatory." Cornil, Cazin[83] and others also concluded that the tumors produced by parasites were of this nature. Even the cancers which Doyen obtained by inoculations with a supposed specific microbe, were found by Weinberg,[84] of the Pasteur Institute, after a careful examination, and also by Cornil, to be an inflammatory "proliferation of tissue." This conclusion indicates the cancerous nature of the growth, since the main landmarks upon which it could be based were the intense hyperæmia, the equally marked leucocytosis and the granulation tissue, all of which, however, as previously stated, indicate an entirely different process, *i.e.*, excessive nutrition through the accumulation of blood and cells. Indeed, as stated by Councilman,[65] the characteristic of cancerous growths is that they are capable of attracting to themselves a supply of nourishment at the expense of the surrounding tissue, and necessarily, I may add, of the body at large. This is an attribute of all cancerous growths, whether sporadic or due to transplantation or inoculation.

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[67] Cited by Warren: *Loc. cit.*

[68] Borrel: Ann. de l'Inst. Pasteur, vol. xvii, p. 81, 1903.

[69] Borrmann: Münch. med. Woch., Bd. lii, S. 2028, 1905.

[70] Jensen: Hospitalstidende, vol. xi, pp. 549, 581, 1903.

[71] Bashford: Lancet, Apr. 1, 1905.

[72] Sir William Church: *Ibid.*, July 8, 1905.

[73] Leo Loeb: Jour. of Med. Research, vol. iii, p. 44, 1902; vol. v., p. 467, 1903.

[74] Senn: Jour. Amer. Med. Assoc., Apr. 28, 1906.

[75] Sanfelice: Annales de micrographie, 1894; Riforma medica, vol. xx, p. 981, 1904.

[76] Roswell Park: Med. Record, May 18, 1901.

[77] Gaylord: Trans. Med. Soc. of State of New York, Jan., 1899.

[78] Doyen: Brit. Med. Jour., Dec. 17, 1904.

[79] Sticker: Zeit. f. Krebsforschung, Bd. i, S. 413, 1904.

[80] Vischer: Bruns' Beitr. z. klin. Chir., Bd. xlii, S. 617, 1904.

[81] Schmidt: Münch. med. Woch., Bd. liii, S. 162, 1906.

[82] Lazarus-Barlow: "Manual of Gen. Pathol.," second edition, p. 504, 1904.

[83] Cazin: Revue des mal. cancéreuses, Oct. 20, 1895.

[84] Weinberg: Cited by R. S. Williams: Lancet, Apr. 8, 1905.

This does not alter the fact, however, that as Orth[66] declared recently, "no one up to the present time has produced proof that carcinoma is of parasitic origin." All that can be said is that certain parasites can be included among the many factors of divers kinds that are capable of irritating the cellular elements which act as foci for the development of malignant growths. This accounts for an important corroborative fact adduced by the supporters of the parasitic doctrine, viz., that it clings to districts, buildings, or groups of buildings, that it may occur epidemically, as observed by Hvoslef[67] (all the cases being in aged subjects) and others, and that it has, though rarely, been communicated. With various exogenous and endogenous agents as pathogenic elements, quarters inhabited by cancerous subjects may readily become intermediary. This applies as well to direct contamination through contact with a malignant growth, since, as shown later, vestiges of such growths, or even their juices after filtration, can start a malignant process in an ulcerated mucous membrane. As this implicates the tongue, lips, œsophagus, uterus, etc., while an area of ulceration may be extremely small and still constitute a vulnerable spot, it is probable that more cancers are thus communicated than is now realised, irrespective of any specific parasite as cause.

Cancer cells, when placed in appropriate surroundings, retain their vitality several days, and when transplanted, continue to divide and multiply, preserving the characters of the original tumor. This accounts for the fact that malignant tumors can develop in regions remote from the original growths. The predilection of the lymphatic glands to metastasis, however, is due to the relative viability of these cells in lymph as compared to blood:* While the blood is destructive to cancer-cells, especially when its temperature (*i.e.*, its proteolytic activity*) is above normal, the lymph into which the cells pass on leaving the cancerous mass is not. This is mainly because (1) its temperature is lower than that of the blood, (2) its proteolytic activity is relatively slight and (3) its circulation is extremely slow (4 mm. per second). The cancer-cells being comparatively immune in lymph, they readily reach the lymph-glands which occur in the path of the lymph-streams and tributaries emanating from the main tumor.* As all tissues are permeated by lymphatic vessels, these afford ready channels for cancer-cells to every part of the body, a fact which accounts for the frequent occurrence of metastatic growths in regions remote from the original cancerous mass, and in all kinds of tissues. This is facilitated, moreover, by the fact that the cancerous fluids can also provoke the transformation of an aggregate of benign adventitious cells, the edges of an ulcer, etc., into a malignant growth and likewise cause the development of the latter when injected into the tissues.

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* *Author's conclusion.*

[65] Councilman: Boston Med. and Surg. Jour., Sept. 14, 1899.

[66] Orth: Berl. klin. Woch., Bd. xlii, S. 281, 326, 1905.

[67] Hvoslef: Tidsskrift f. d. Norske Laegeforening, No. 17, 1902.

Not every accessory growth should be regarded as metastatic, however, since cancers of a similar kind and even of different kinds have been known to develop in the same subject simultaneously.

Bashford[58] states that when cancer is successfully inoculated from one animal to another, "a few parenchyma cells retain their vitality and continue to divide and multiply, giving rise to large tumors at the site of inoculation;" the new stroma formed "assumes the distinctive features of the original stroma," the new tumor, therefore, being "exactly like the original one." Indeed, as emphasized by Albrecht,[59] metastatic growths in human cancer cases may even functionate, as do the organs from which they are derived.

The viability of detached tissues accounts for the resumption of their functions. Thus, Ljunggren[60] found that when carefully sterilized, bits of human skin could be preserved in sterile human ascitic fluids for months, and that the cutaneous cells retained their vitality. Transplanted pieces which had been in this fluid one month, subsequently showed marked proliferation of epithelial cells and many nuclear figures. The transplanted cells also penetrated into the granulation tissue beneath, as in beginning carcinoma. Jensen[61] observed a similar resistance in cancer cells, some living twelve days, isolated, at the room temperature. In the blood, however, matters were different: he found that at the temperature of the body they perished in twenty-four hours, and that at temperature *above* the normal they rapidly lost their vitality. Metastasis, therefore, can occur only under certain conditions, for it is only *when* or *where* the temperature is normal or below normal, that detached cancer cells can safely run the gauntlet of the blood's destructive action and reach a spot where they may, as it were, take root and grow. Indeed, as stated by Bashford,[62] the transmission of cancer differs from all known processes of infection: "the tissues of the new hosts do not acquire any cancerous properties; they merely react to the presence of cancer cells and supply them with nourishment." As explained in the text, a field where detached cancer cells are not endangered is unfortunately available as soon as they leave the tumor, viz., the lymphatic vessels themselves, the normal channels for all detritus, and which serve also for their general distribution, as stated below.

Even apart from the direct development of a tumor by transplantation thus provoked, a lesion anywhere, and characterized by an agglomeration of adventitious cells, may become the starting point of malignant growth when these cancerous vestiges are available. Thus Hemmeter[53] obtained gastric carcinoma in dogs affected with experimental peptic ulcer, by inoculating the animals with particles of canine adenocarcinoma. More striking, however, is the fact that he obtained similar results by injecting a sterile and cell-free filtrate of a similar growth. As Mayet[54] also obtained a splenic sarcoma by injections of a filtrate of a uterine myoma—a frequent precursor of cancer—it is evident that a fluid derived from the cancerous mass, and not necessarily cancer tissue, can start the malignant process. The ease with which the poison may be distributed being thus greatly increased, almost any preëxisting lesion in any part of the body is exposed to contamination, and may thus become the seat of cancer as was the case in Hemmeter's animals.

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[58] Bashford: Brit. Med. Jour., Dec. 9, 1905.
[59] Albrecht: Münch. med. Woch., Bd. xlix, S. 1135, 1902.
[60] Ljunggren: Cited by Hektoen: "Progressive Medicine," p. 226, Mar., 1899
[61] Jensen: Centralbl. f. Bakt., Bd. xxxiv, S. 122, 1903.
[62] Bashford: Brit. Med. Jour., Dec. 9, 1905.

The *cancerous cachexia* is due to hæmolysis, the result, in turn, of the excessive proteolytic activity of the blood.* Both the red corpuscles and the hæmoglobin are actively destroyed, this morbid process beginning soon after the cancer begins to grow. The presence in the blood of an excess of adrenoxidase—and therefore of auto-antitoxin, to which this morbid process is due—provokes likewise an exaggerated vasotonus by stimulating unduly and directly the muscular coat of all arteries.* As a result of the vasoconstriction thus produced, the blood-serum is forced into the capillary system and lymphatics, causing various manifestations of œdema, anasarca, hydrothorax, puffiness, etc.* After death the caliber of the vessels is found considerably reduced, owing to the prolonged constriction to which they are subjected during life.* This also predisposes the patient to congestive disorders; hence the pulmonary congestion, the neuritis, phlebitis and kindred disorders often met with.* The excess of adrenoxidase is likewise shown by the tendency to thrombosis observed in these cases, adrenoxidase being, as we have seen, the blood's fibrin-ferment.*

The prolonged strain imposed upon the adrenal system finally causes it to become functionally weakened.* This condition is aggravated when the tumor is the seat of ulceration, by auto-intoxication, owing to the accumulation in the blood of detritus and bacteria from the putrifying mass. Death occurs, unless a fatal intercurrent disease appear, from asthenia, the typical mode of death when the adrenal center becomes paralyzed.*

The cancerous cachexia is now attributed to the direct action of poisons derived from the cancer upon the tissues, causing their degeneration. That this is due to hæmolysis, however, is shown in various ways. As far back as 1843, Andral and Simon found the red corpuscles greatly reduced even during the early stages of the disease, a fact confirmed by Hayem and others. Roger Williams,[95] who refers to these authors, also states that "the red blood-corpuscles show signs of progressive deterioration and destruction. A marked diminution of the hæmoglobin was also shown to exist by Quinquaud, a fact confirmed by Chudowsky[96] after examining the blood of 51 cases, Donati[97] and others. Roger Williams says, moreover, that "a thousand grams of normal blood contain about 125 grams of this substance, whereas in cancer cases the amount often does not exceed 25 grams." He compares the condition to that which prevails in pernicious anæmia, which, as we will see, is due to hæmolysis. Finally, Kullmann[98] found recently that freshly-drawn blood of cancerous subjects contained a hæmolytic substance, and that it acquired especial activity when the cellular elements were present. That the only hæmolytic substance is auto-antitoxin, we have seen.

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* *Author's conclusion.*

[53] Hemmeter: Amer. Jour. Med. Sci., Apr., 1903.

[54] Mayet: C. r. de l'Acad. d. sci., May 29, 1905.

Other phenomena which are now misinterpreted are the serous effusions, the anasarca, etc. That they are due to general vasoconstriction is shown by the fact referred to by Roger Williams, that in cases that have run their natural course, "smallness of the heart, aorta and arterial trunks" is "observed post-mortem," and that as shown experimentally by Louis (1846), the "total quantity" of altered blood is "notably diminished." Considerable of their serum having passed into the subcutaneous tissues, the chest, etc., œdematous effusions occur. The cause of the excessive vasoconstriction becomes apparent also, when the direct action of the unusual quantity of the auto-antitoxin on muscular coats of the vessels is taken into account, as stated in the text. This effect should, however, also be manifest in the other muscles of the body. Klippel[99] observed that notwithstanding the wasting there was marked reflex hyperexcitability of the muscles. The excess of all three constituents of the auto-antitoxin is likewise shown by the paradoxical phenomenon recently observed by Sticker,[100] that when cancer had been successfully transplanted in dogs, these animals were immune to further inoculation. Indeed, the Cancer Research Commission also found recently, according to Bashford,[101] that "an injection of healthy blood may protect mice against the subsequent inoculation of Jensen's tumor being successful." The reason for this becomes self-evident in view of the identity of the body's auto-protective agency, the auto-antitoxin that the blood contains.

That the adrenal should finally yield, under these conditions, is obvious. Nepveu[102] found what lymphatics were present filled with detritus of various kinds, and epithelium. The morbid effects of the detritus are generally recognized. Elfer[103] compares the putrifying process to that which occurs in plants having parasitic excrescences. The roots of some of these, through various bacteria, including the bacillus amylobacter, become centers of infection which, owing to the cacodyle, give out a repulsive odor. In human cancer, the corresponding ulceration is due to pyogenic and other bacteria. Thus, Wlaëff,[104] found among others, the proteus septicus hominis and the bacillus coli communis. That these organisms enter the blood-stream was shown by

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[95] Roger Williams: Edinburgh Med. Jour., June, 1897.

[96] Chudowsky: La méd. moderne, vol. vi, p. 151, 1895.

[97] Donati: Giorn. della r. Accad. di Med. d. Torino, June, 1901.

[98] Kullmann: Zeit. f. klin. Med., Bd. liii, S. 293, 1904.

[99] Klippel: *Loc. cit.*

[100] Sticker: Zeit. f. Krebsforschung, Bd. i, S. 413, 1904.

[101] Bashford: Brit. Med. Jour., July 28, 1906.

[102] Nepveu: Marseille-médical, Jan. 15, 1898.

[103] Elfer: Le correspondant médical, Aug., 1895.

[104] Wlaëff: Jour. de méd. de Paris, vol. xvi, pp. 255, 262, 1904.

Maragliano.[illegible] He examined the blood of 33 cancerous patients, and although the strictest antiseptic precautions were taken in each instance, he found staphylococci of various kinds in 9 instances. These were all cases in which ulceration had occurred, while no bacteria were found in the blood when such ulceration was absent. The general course of this additional morbid process is precisely that depicted by Roger Williams. "When ulceration sets in and the wound gets invaded by microbes," writes this observer, "the ordinary symptoms of septic infection may be *added* to those of the cancerous cachexia. Considering the putridity that characterises these ulcerating cancers, especially when the uterus is the part affected, septic complications are remarkably rare; but no doubt in certain cases, they contribute their quota to the *ensemble* of symptoms. Hæmorrhages and suppurations further impoverish the blood and weaken the patient. At length, if not cut off by some intercurrent complication, death results from *asthenia*."

Treatment.—*Removal of the tumor* and of all contaminated glands or metastatic growths is followed by prompt recovery, even the cachectic phenomena disappearing in practically all cases. This procedure, when practicable without endangering the patient's life or producing unusually distressing deformities, *is still,* and rightly, too, *the method of choice,* until some non-surgical measure will have proven itself as reliable. Potent reasons urge, however, the need of such a measure: besides the desirability of avoiding mutilation, the impossibility to operate in some cases, the delay which dread of surgical procedures inspires, etc., there is the undeniable fact that removal of the growth serves but to defer its fatal effects in the vast majority of cases, an assertion but too clearly sustained by the ever-growing death-rate. The functions of the endocrines not only open a new field for the study of cancer but they suggest more encouraging lines of treatment.

A cancer, in the light of the foregoing facts, is initiated, nourished and caused to grow by blood constituents which, as agents of the organism's auto-protective mechanism, should, in reality, have destroyed it from the start.* Owing to senility or other debilitating conditions, however, the defensive process, which requires an *excess* of auto-antitoxin, is inadequate; and mere nutrition, with mitotic proliferation of cells, *i.e.,* growth, results, because the blood's auto-antitoxin happens to be composed of the identical substances which, under normal conditions, nourish the tissues.* Our aim, therefore, should be to raise, if possible, the functional efficiency of the body's defensive resources by means of agents which, by increasing markedly the functions of the adrenal system, augment correspondingly the proportion of auto-antitoxin in the blood and other body-fluids.* All the agents studied in the eighteenth and nineteenth chapters, and others not analyzed in the present work, are available to attain this end.* *Thyroid gland* occupies a prominent place among them, the most satisfactory being desiccated thyroid.

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* *Author's conclusion.*

[illegible] Maragliano: Gazz. degli Osped., Jan. 12, 1901.

Thyroid extract was used in cancer as an adjunct to oöphorectomy, some years ago, by Beatson,[106] Stanley Boyd,[107] Dorland,[108] and others; but as removal of the ovaries might have accounted for the beneficial results noted, these reports can hardly be taken as guide. It was first used alone in cancer (and before Beatson) by Robert Bell,[109] with success. Recently,[110] he stated that several of the recoveries were of over nine years' standing, although they included cases of mammary and uterine cancer. Page and Bishop[111] caused the entire disappearance of a carcinoma of the breast by the use of the gland alone, beginning with 3 grains (0.2 gm.) and increasing until 15 grains (1 gm.) were given daily. At the time of the report, two and one-half years later, was well, and no trace of the cancer could be discovered. Dennis[112] also obtained more benefit from the use of thyroid gland than from any other agent, while H. A. Beaver,[113] in a desperate case of carcinoma (also recognized as such by Sir Francis Laking) nearing its end and attended by great suffering, obtained results "little short of marvelous." He states that "convalescence began immediately, so that by the end of January [the thyroid extract, 5 grains (0.33 gm.), quickly increased to 20 grains (1.33 gms.) daily, having been begun at the end of November] the patient was up and free from pain." The following October she "was quite well and was following an active life." E. Hughes Jones[114] reports a cure of 11 years' standing in a woman aged 61 years, and R. H. Woods[114a] the complete disappearance of a laryngeal cancer, under 3 grains of thyroid three times daily. He refers to Sir Charles Ball as having cured 2 cases of inoperable cancerous lymphatic glands. We have seen that Naamé (1921) also found it curative.

The prevailing empirical use of thyroid gland fails to afford the best results* and exposes the patient to complications,* for the following reasons: (1) The vigor with which large doses enhance oxygenation and catabolism through the adrenal system, not only in the body at large, but in the cancerous mass itself, entails an accumulation of waste-products in the lymphatics and blood-vessels beyond the excretory capacity of the kidneys. The indiscriminate use of such doses, therefore, exposes the patient to nephritis which may prove fatal; (2) the use of thyroid gland alone, by raising metabolic activity in the organism and in the growth, involves the corresponding consumption of the blood's sodium chloride and, though in a less degree, its alkaline salts.* If these are not replaced, the patient's vital functions become greatly depressed; and osmosis being deficient, he becomes readily vulnerable to intercurrent diseases, while the beneficial influence of the extract is thwarted, through the fact that the trypsin, the active agent of auto-antitoxin, loses its power in the absence of sodium chloride; (3) excessive, *i.e.*, still greater doses, by causing a correspondingly great quantity of thyroiodase to accumulate in the blood, soon influences the depressor nerve, and the functions of the patient's pituitary and thyroid bodies being inhibited, the stimulating action of the extract on the test-organ and adrenal center (through which its beneficial effects are produced) is prevented.*

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* *Author's conclusion.*

[106] Beatson: Brit. Med. Jour., June 6, 1896.

[107] Stanley Boyd: *Ibid.*, Oct. 2, 1897.

[108] Dorland: Therap. Gaz., May 15, 1899.

[109] Robert Bell: Trans. Brit. Gynec. Soc., vol. v, 1896.

[110] Robert Bell: Brit. Med. Jour., Jan. 16, 1904.

[111] Page and Bishop: Lancet, May 28, 1898.

[112] Dennis: Jour. Amer. Med. Assoc., Oct. 19, 1901.

[113] H. A. Beaver: Brit. Med. Jour., Feb. 1, 1902.

[114] Jones: Brit. Med. Jour., Feb. 25, 1911.

[114a] Woods: London letter. N. Y. Med. Jour., July. 1911.

The dose of desiccated thyroid should, therefore, be small to begin with: 1 grain (0.065 gm.) three times daily, in a subject of average health apart from the presence of the growth, this quantity being gradually increased by one grain (0.065 gm.) weekly, until 3 grains (0.2 gm.) are taken after each of the three meals—provided, however he does not complain of rheumatic pains (which indicate excessive metabolism), and his urine remains approximately normal, albuminuria being only regarded as abnormal when marked.*

To preserve the fluidity of the blood, facilitate the excretion of catabolic wastes and protect the kidneys by causing the specific gravity of the urine to remain low, a quart of some *mineral water*, such as Ballardvale, Londonderry Lithia, etc., should be drunk in the twenty-four hours.* This applies only, however, to patients whose diet is normal, *i.e.*, who ingest through its intermediary enough sodium chloride and alkaline salts to satisfy the needs of the organism.*

In fully developed cancer, the blood as a whole is deficient in *sodium chloride*. As the proteolytic activity of trypsin requires a fixed proportion of this salt—especially since it facilitates osmosis and tissue-metabolism—it should be given as an adjuvant to the thyroid extract.* Its use assumes additional importance when the fever is marked, when the patient is on a milk diet, or when but little food is taken, since the latter must compensate the body for the sodium chloride excreted in the urine,* over one-half ounce (14 gms.) daily. The indications for its use are similar to those in febrile diseases,[115] the quantity ingested being regulated by the degree of pyrexia.

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* *Author's conclusion.*

In advanced cases, the renal functions are usually impaired. Sodium chloride under these conditions provokes œdema. It is also contraindicated if any form of œdema is already present. Plain or mineral water should then be used instead, as in the earlier stages of the disease.*

The fact that excessive doses of thyroid gland tend to aggravate the renal disorders to which cancerous subjects are liable is made self-evident not only by the well-known fact that it increases markedly the urea excretion, but also by several cases reported. The use of considerable pure or mineral water to insure adequate fluidity of the blood and to protect the kidneys is of considerable importance. In two of my cases it sufficed (without thyroid) to cause retrogression of the growth. In one of these, a breast cancer in the initial stages, about to be removed under the advice of two surgeons, there has been no recurrence, though six years have elapsed. The patient (æt. 74) faithfully continues drinking one quart of (still) mineral water daily. This points clearly to the importance of osmosis in the curative process.

The relationship between the functional efficiency of trypsin (the active proteolytic agent in auto-antitoxin) and sodium chloride is well-known to physiologists. Thus Halliburton[116] states that pancreatic juice taken from a temporary fistula, contains 7.35 parts of sodium chloride in a thousand. As this is almost exactly the proportion in normal saline solution, trypsin, the active ferment in pancreatic juice, must require this proportion to exercise its proteolytic action most actively. This constitutes, therefore, an important feature in the treatment of cancer.

Again, Von den Velden[117] has shown that free hydrochloric acid is absent in nearly all cases of gastric cancer. Osler[118] states that "of 94 cases in which the contents were examined, in 84 free HCl was absent." This is not due to the local disease, for Moore, Roaf and Whitley[119] found recently that in practically all cases of cancer, and *wherever located*, free hydrochloric acid is either absent from the gastric contents or greatly reduced in quantity. Now, as shown by the experiments of Voit and Cahn, "the chlorides present in the blood-plasma are the source of the acid."[120] Hammarsten[121] also states that "there can be no doubt that the hydrochloric acid of the gastric juice originates from the chlorides of the blood." It is evident, such being the case, that the blood, *as a whole*, is deficient in sodium chloride. In the light of evidence previously adduced, therefore, the osmotic properties of the plasma and the activity of the adrenoxidase and trypsin are all impaired in cancer.

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* *Author's conclusion.*

[115] *Cf.* this volume, p. 1367.

[116] Halliburton: Schäfer's "T. B. of Physiol.," vol. i, p. 77, 1898.

[117] Von den Velden: Deut. Archiv f. klin. Med., Bd. xxiii, S. 369, 1879.

[118] Osler: "Practice," sixth edition, p. 483, 1905.

[119] Moore, Roaf and Whitley: Lancet, Dec. 16, 1905.

[120] Voit and Cahn: Cited by Moore: Schäfer's "T. B. of Physiol.," vol. i, p. 358, 1898.

[121] Hammarsten: "T. B. of Physiol.-Chem.," fourth edition, p. 306, 1904.

I recommended the use of saline solution simultaneously with thyroid gland and the x-ray, in the first volume (January, 1903), also calling attention to the fact that "the curative process requires alkaline salts" to insure the full activity of the tryptic intraphagocytic digestion"—besides that of the cancerous cells carried on by the plasma's autolytic constituents. This in a measure accounts for the beneficial results obtained with sodium chloride alone by Rost.[122] Freund[123] also found that the introduction of an alkaline fluid into arterial channels leading to the growth proved beneficial. But in view of the facts adduced above, it is evident that salt alone cannot prove curative.

Its contraindication in advanced cases is shown by the fact that Glosser and Frisbie[124] found experimentally that while a normal subject could ingest large quantities of sodium chloride without evil effect, cancer patients showed œdema when the chloride consumption was increased—a fact which they ascribe to the impairment of renal excretion. Indeed, œdema may occur in its various forms, as we have seen, when the cachectic period is reached—an indication that the kidneys are the seat of inflammatory lesions caused by the excessive functional activity imposed upon them and the local effects of toxic wastes.

X-ray and radium cause a rise of temperature and hyperæmia in the growth, thus causing the proteolytic activity of the auto-antitoxin (*i.e.*, its trypsin) in its blood.* The penetration of the x-rays is greater than that of radium; hence the great efficacy of the former. The frequent failures observed, however, are due to the paucity of auto-antitoxin in the blood.* Thyroid gland should be used simultaneously, therefore, in the manner indicated above.* *Cataphoresis* may likewise be advantageously employed in conjunction with thyroid gland and the use of fluids.

That the x-ray method alone may be effective both in sarcoma and epithelioma, has been shown by Morton, Allen, Pusey, Pfahler, Leonard, Skinner, Beck and others. Even here, breaking down of the tissues by the trypsin in the cancer is evidently the curative process. As noted by most clinicians, congestion is a prominent feature of the effect produced, the local temperature, as observed by Carl Beck,[125] being somewhat higher. As stated by Skinner,[126] moreover, "the effect of the x-ray light is due to a stimulation of the reparative functions of the tissues dependent on an inflammatory reaction," but *how* is this carried out? "Its destructive influence," continues Skinner, "is always exhibited on tissues which are low in vitality." The need of a destructive agent in the process asserts itself, however, and trypsin, we have seen, is present in large quantities in cancerous growths.

I advised the concomitant use of x-ray and thyroid gland over seven years ago.[127] Since then, Am Ende,[128] having used it in several instances, obtained beneficial results in two cases which, under x-rays alone, had failed. He mentions three cases which were proving rebellious to x-ray treatment and were given thyroid by R. T. Morris, in addition to the rays. "All three responded promptly," two being cured and the third improved. Another case of Morris's, an extensive recurrent carcinoma of the breast, also ended in cure under the combined treatment. Am Ende[129] recently reported seven cases in which recurrent growths were markedly reduced, some disappearing completely, by means of the combined use of a fluid extract of sheep's thyroid and radium or x-rays. In one instance, a case of adeno-carcinoma of the sigmoid flexure and rectum, diagnosed by laparotomy, and abandoned as lethal, normal health was restored.

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* *Author's conclusion.*

[122] Rost: Alkaloidal Clinic, Aug., 1909.

[123] Freund: *Loc. cit.*

[124] Glosser and Frisbie: Jour. Amer. Med. Assoc., Feb. 24, 1906.

[125] Carl Beck: N. Y. Med. Jour., May 24, 1902.

[126] Skinner: Jour. Amer. Med. Assoc., Jan. 17, 1903.

[127] Sajous: Monthly Cyclo. of Pract. Med., May, 1908.

[128] Am Ende: Amer. Jour. of Surg., Aug., 1908.

In one case radium was used with thyroid by Am Ende, the result being "considerable constitutional betterment," besides the improvement of local symptoms. The action of radium is similar to that of x-rays, but as emphasized by Perthes[130] and Exner,[131] its influence does not extend much beyond 2 or 3 centimeters from the surface. The influence of this on its therapeutic value is well shown by the following summary, by Catharine Macfarlane,[132] of the results obtained by various clinicians: "13 rodent ulcers cured; 14 epidermoid cancers cured; 1 malignant wart cured; 11 cases of cancer of the œsophagus slightly improved; 1 sarcoma cured; 27 carcinomas unaffected; 1 malignant wart unaffected; 1 malignant mole unaffected; 1 rodent ulcer unaffected." Diminutive growths may be destroyed, therefore; thus, in 19 mice-cancers ranging from a pea to a bean in size, Apolant[133] obtained complete retrogression in 11, and reduction to mere traces in the rest. Morton, Lassar[134] and others have reported cures in human subjects, but, on the whole, radium is not as effective as the x-rays. Plimmer,[135] for example, tried radium in 17 cases, with but slight, if any, beneficial effect. In nearly every instance, however, the growth is said to have "blistered" or "reddened"—evidence to the effect that it provokes local hyperæmia—a well-known fact. When radium acts directly on ferments it soon destroys them, but Neuberg[136] has shown that when of two fragments of the same cancer, one is exposed to the action of radium and the other is not, the first will undergo disintegration twice as fast as the second. The wealth of these growths in trypsin, and the heat-energy supplied by the radium, account for this effect, as in the case of the x-ray. Indeed, here, there being no circulation of blood, the heat evoked by the radium alone becomes the energizing agent of the ferment. The use of cataphoresis, as practiced by Betton Massey, suggests itself as probably more effective than either the x-rays or radium, since it promotes disintegration of the growth, as does thyroid extract.

Thyroid gland is always indicated when the x-ray or radium is used, to prevent metastasis.* The proportion of auto-antitoxin in the blood and the tumor itself being increased, the cellular fragments and the soluble poisons liberated during the disintegration of the malignant tissues are themselves more perfectly broken down, thus reducing the chances of metastasis in proportion.*

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* *Author's conclusion.*

[129] Am Ende: Jour. of Advanced Therap., Apr., 1907.

[130] Perthes: Verh. d. Deut. Gesellschaft f. Chir., Bd. ii, S. 398, 1904.

[131] Exner: Deut. Zeit. f. Chir., Bd. lxxv, S. 379, 1904.

[132] Catharine Macfarlane: Amer. Medicine, Apr., 1906.

[133] Apolant: Deut. med. Woch., Bd. xxx, S. 454, 1904.

[134] Lassar: Berl. klin. Woch., Bd. xli, S. 534, 1904.

[135] Plimmer: Lancet, Apr. 16, 1904.

[136] Neuberg: Zeit. f. Krebsforschung, Bd. ii, S. 171, 1904.

Allen, Coley[137] and other observers have found that metastasis occurred more frequently under the x-ray treatment than without it. This is readily explained by the fact that as the mass is being broken down, fragments and toxic juices (capable, we have seen, of causing metastasis in proximate or remote tissues) are freed into the lymph spaces in unusual quantities. The proportion of auto-antitoxin in the blood being in no way increased by the local treatment, the process of implantation or intrinsic inoculation is not antagonized. By powerfully stimulating the adrenal center, thyroid gland greatly increases not only the proteolytic activity of the blood and the proportion of phagocytes, but also that of the cancerous mass itself. The detached fragments, cells, and soluble poisons are thus, from the start, either reduced to the condition of benign wastes, or their activity as living cells or as bio-chemical elements is greatly diminished.

The local application of the adrenal principle favors the curative process. *Adrenalin* in 1: 1000 solution, painted or swabbed over the surface of the growth relieves pain, arrests hæmorrhage and even tends, by causing constriction of the vessels, to cause partial retrogression of the growth. Injection of 10 minims of the same solution into the tumors enhances further the latter effect; but the injections should be given under strict asepsis, and after carefully sterilizing the surface.

The local effects of adrenalin in this connection was observed by C. Fiesinger,[138] who attributed them to its effect on vessels of the neoplasm. In cancer of the rectum, he found that painting twice daily with 30 to 100 drops of a 1: 1000 solution of adrenalin in a tablespoonful of water decreased the rectitis, checked the discharge and brought about a temporary diminution of the growth. Mahu[139] had previously obtained prompt results by simply painting the growth with the 1: 1000 solution. The neoplasm partially retrogressed; then remained stationary and free from pain or hæmorrhage, the patient being in apparently perfect health. In four other cases the results were also satisfactory. Berdier and Falabert[140] tried injections in advanced cases and found that they caused diminution of the tumor and of the adjoining glands, abolishing pain and increasing the patient's weight. The injections were made into the tumor or, when this was inaccessible, into the arm or over the organ involved. J. E. Rhodes[141] reported a case of inoperable nasopharyngeal sarcoma in which the injection of adrenalin into the growth together with local swabbing and spraying caused marked reduction in size and alleviated the pain, though the patient's life was not prolonged. J. Price-Brown[142] also found that adrenalin checked the circulation in sarcoma and lessened bleeding.

Adrenal gland, the *glandulæ suprarenales siccæ* of the U. S. P., is of advantage in these cases to prevent anæmia by supplying the blood with the oxidizing constituent of the hæmoglobin.

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* *Author's conclusion.*

[137] Coley: Amer. Jour. Med. Sci., Mar., 1906.

[138] Fiesinger: Journal des Praticiens, Apr. 23, 1902.

[139] Mahu: La Presse Médicale, Apr. 4, 1903.

[140] Berdier and Falabert: Semana Medica; Jour. Amer. Med. Assoc., Mar. 25, 1905.

[141] Rhodes: Jour. Amer. Med. Assoc., Aug. 11, 1906.

[142] Price-Brown: Med. Record, Oct. 6, 1906.

Three grains three times daily with *iron*, preferably Blaud's pill, 1 grain, prolong life by retarding the cancerous cachexia.

The usefulness of adrenal gland in this connection was illustrated by one of my cases of advanced uterine cancer, in which life was considerably prolonged, improvement of the patient's condition having become manifest soon after the use of the gland had been begun. It seemed also to prevent severe pain, doubtless by causing constriction of the arterioles, thus reducing the local hyperæmia and swelling. The patient died, in fact, without knowing that she had suffered from cancer.

The simultaneous use of *radium, thyroid gland* 1½ grains and *hypophysis sicca* 1/10 grain, the two latter three times a day further improves the likelihood of recovery.

The creation of the Radium Institute in Paris has rendered possible a closer study of the technique, and, as a result, the curative value of radium has shown itself to be greater than had been generally supposed. Wickham,[146] a clinician of the first order, has observed remarkable results in a variety of cases, including epithelioma not only of the surface, but of such organs as the breast. By means of appropriate metal shields he regulates the activity of the radium and employs the *beta* and *gamma* rays only for deep-seated growths. On the other hand, my own experience with opotherapy has amply demonstrated their helpful influence in malignant growths.

Various organic extracts, including *testicular juice, lymph-gland juice,* an extract of *ram's testicles,* and *thymus extract* have been tried. None of these substances, however, are endowed with the specific properties of thyroid extract. Even *adrenalin* is useless given internally, since it is oxidized before it reaches the tumor at all. *Iodine* and the *iodides* have been extolled by various observers. The fact that thyroidase is an organic compound of iodine points to the iodides, especially sodium iodide, as a substitute when thyroid gland is not well borne.*

Mikhailoff considers potassium iodide a specific in cancer. In a preliminary communication[147] he announced that he had obtained favorable results with this treatment. He recently reported a case of cancer of the œsophagus treated by potassium iodide with marked success. Many other remedies have been tried, but their enumeration would be out of place in this work.

Although the various "cancer sera" or "*antitoxins*" are composed of the constituents of auto-antitoxin, the quantity introduced is inadequate to produce more than fleeting effects. A continuous exogenous supply is necessary to replace the auto-antitoxin formed under the influence of adrenal stimulants.*

More efficacious are the various *toxins*, especially *Coley's* mixed toxins of erysipelas and bacillus prodigiosus. They also produce disintegration of the growth by stimulating the adrenal center, and through it, therefore, the formation of auto-antitoxin.* Toxins are only efficacious in sarcoma, however, because this variety of cancer occurs usually in subjects who are young, and whose adrenal system is more vigorous; and because the greater vascular supply of the growths themselves renders them more vulnerable to the disintegrating action of the auto-antitoxin.* For carcinoma, however, the action of toxins on the adrenal center is inadequate and less efficacious than that of thyroid extract.* Their value is sufficient, however, to warrant their use in sarcoma, especially with x-rays, which distinctly enhance their effects. (See also p. 757, vol. i.)

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* *Author's conclusion.*

[146] Brit. Jour. of Dermatology, July, 1909.

[147] Mikhailoff: Roussky Vratch, Dec., 1908.

The treatment by auto-antitoxin was introduced by Richet and Héricourt, of Paris, in 1895, who obtained encouraging results in cancer patients, by injecting blood from animals previously injected with an extract of cancer tissue. Jensen, in 1901, cured cancerous mice by injections of blood from rabbits previously injected, a result also obtained by Clowes and Baeslack[148] and others. Leyden and Blumenthal[149] reported positive results both in dogs and man by means of serum derived from goats treated months with injections of carcinoma. Gaylord, Clowes and Baeslack[150] then showed that the serum of mice treated with immunizing serum was capable of causing the disappearance of small tumors and checking the growth of the larger ones. A number of sera have been introduced by as many investigators, all giving results similar to those recited above. Tuffier[151] found that any one of them injected in turn into a cancer patient causes retrogression of the lesions to a certain extent and improvement of the clinical picture, but these beneficial effects become gradually less. At times, no beneficial effect is obtained, as in cases reported by D'Arcy Power.[152] Analysis of these cases in the light of my views, however, shows that the curative process had started, and identifies the nature of the process; thus he complains that it caused an *inflammation in the growths*. The disease progressed to a fatal issue while the injections were being given.

The treatment by toxins, which, like thyroid, causes adrenal stimulation, may be illustrated by the treatment of inoperable sarcoma by mixed toxins of erysipelas and bacillus prodigiosus as practiced by W. B. Coley, of New York, since 1892, the use of the first-named toxin having been suggested by the inadvertent cure of a severe case of very malignant sarcoma, which had recurred four times, by two attacks of erysipelas. In a recent paper to which the reader is referred,[153] Coley gives statistics of a large number of cases treated by himself and by other surgeons, showing a large proportion of recoveries (the patients being from 3 to 13 years old). That the curative process is due to great increase of auto-antitoxin in the blood, is shown by the fact that results are linked with the temperature ratio. "The dose should be gradually increased," writes Coley, "until a chill occurs (one-half to two hours after injection), followed by a temperature of 101° to 103°

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* *Author's conclusion.*

[148] Clowes and Baeslack: Med. News, Nov. 18, 1905.

[149] Leyden and Blumenthal: Deut. med. Woch., June 11, 1902.

[150] Gaylord, Clowes and Baeslack: Med. News, Jan. 14, 1905.

[151] Tuffier: Presse médical, vol. xii, p. 27, 1905.

[152] D'Arcy Power: Brit. Med. Jour., Feb. 6, 1904.

[153] Coley: *Loc. cit.*

or 104° F." (some cases mentioned reaching 105?), "the destructive process in the growth being manifested in most cases by "breaking down"—precisely the effect produced by thyroid extract and trypsin. Schmittle[154] observed that the temperature kept high after the injection of toxins unless brought down by an antipyretic. The use of toxins is not devoid of risk, however. Marmaduke Shield[155] observed a case which, though there was "undoubted and apparent disappearance of the growth," a fact which he ascribes "purely to inflammatory action," ended in death, the autopsy showing the signs of "general pyæmia."

In sarcoma the x-ray method is of but little value. Coley gave it a careful trial in 68 cases, and obtained very unsatisfactory results, and prompt recurrence. When, however, the toxins were injected in addition to the x-ray treatment, the effect was very marked, recovery occurring in two out of six instances. This indicates that it is *through the blood* that the curative influence is exerted—as it is when the thyroid is used.

The local application on the ulcerated surface of a 1 per 1000 solution of *adrenalin* relieves pain and controls hæmorrhage. The latter effect is also encouraged by thyroid extract, since by stimulating the adrenal center it increases the proportion of fibrin ferment (adrenoxidase) in the blood, and facilitates coagulation.* To asepticize the ulceration and control the fœtor, *formalin* in a 2-per-cent. solution is quite effective when the dressing is changed every six hours.

Fiessinger[156] found that 30 to 100 drops of a 1 to 1000 solution of adrenalin injected with a tablespoonful of water, gave a marked relief in rectal cancer. Mahu[157] used it in the manner indicated above in seven cases, including mammary and rectal cancers. The growths partially retrogressed and remained stationary without causing discomfort. Berdier and de Falabert[158] obtained similar effects by injecting the solution into the growth or in the adjacent tissues. Powell[159] found formalin capable not only of causing the effects mentioned in the text, but also that it tended to promote destruction of the malignant mass. Beneficial effects have also been reported by other observers.

It is important to realize that all these measures have—as with many others tried—proven curative in a very small proportion of cases.

Prophylaxis.—In the light of the foregoing facts, the prevention of cancer would reduce itself to measures calculated to increase the efficiency of the adrenal system.* The "cancer facies," *i.e.*, a peculiar pallor sometimes observed in subjects who subsequently develop cancer (as well as in many who do not), assumes importance if there is a clearly defined hereditary predisposition—a fact which means that congenital hypoactivity of the adrenal system may favor the liability[*] and if the patient is past middle life. The presence of a mole, nævi, papillomata, scars, warts, lingual sores or fissures from the presence of a pipe stem or sharp teeth, chronic uterine disorders, fibromata, chronic ulcers, patches of eczema, etc., may, as we have seen, render a given area liable to the development of cancer. Such lesions, even in a person who shows no hereditary predisposition, when combined with pallor, sallowness, or any condition of the skin which points to deficiency of blood in its capillaries, are prone to malignancy if irritated.[*]

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* *Author's conclusion.*

[154] Schmittle: New Orleans Med. and Surg. Jour., Dec., 1895.

[155] Marmaduke Shield: Brit. Med. Jour., Jan. 23, 1897.

[156] Fiessinger: Jour. des praticiens, Apr. 25, 1903.

[157] Mahu: Presse médical, vol. x, p. 261. 1902.

[158] Berdier and de Falabert: Semana Medica: Jour. Amer. Med. Assoc., Mar. 25, 1905.

[159] Powell: Brit. Med. Jour., May 30, 1903.

In most cases, the cause of the pallor, etc., is due to low vascular tonus, the great vessels of the splanchnic area being engorged, while the peripheral vessels are ischæmic, due, in turn, to hypoactivity of the adrenal system.[*] Here, *strychnine* is of exceeding value, because it activates both the vasomotor and adrenal centers, in doses of $^1/_{40}$ grain (0.0016 gm.) increased to $^1/_{30}$ grain (0.0021 gm.) taken after meals. The *hydrochlorate of quinine,* 2 grains (0.13 gm.), when taken during a meal, does not cause gastric disorders and is likewise effective. If adynamia be present, *thyroid gland* in small doses, 1 grain (0.06 gm.), may either be given alone or with *quinine hydrochlorate* 2 grains (0.12 gm.).[*] A course of the *iodides,* beginning with 5 grains (0.03 gm.) three times daily in a large glassful of water, increasing the dose gradually to 10 grains (0.06 gm.), is also useful, especially if given with the strychnine.[*]

All these remedies, and others studied in the department on Pharmacodynamics, raise the blood-pressure more or less, and a greater volume of blood enriched with auto-antitoxin and phagocytes being caused to circulate in the cutaneous and other capillaries, the normal defensive resources are raised to their normal level.[*] This means that adventitious cellular elements in exposed areas are promptly catabolized by the auto-antitoxin, that the detritus is promptly removed by phagocytes, and that the local process of repair is carried on normally.[*]

In the case of internal cancers, apart from regions that are directly examinable, the larynx, the uterine os, etc., the danger signals are scant and opportunities for prophylactic measures are few. That gall-stones predispose to primary carcinoma of the gall-bladder is well known; hæmorrhages from the stomach, rectum or vagina, in prematurely aged persons, are also familiar precursors of local cancers, especially if associated with emaciation. They may be looked upon, therefore, with sufficient mistrust to warrant prophylactic measures. In these cases, either of the agents previously recommended may be used. *Thyroid gland,* 1 grain (0.13 gm.), and Squibb's *extract of ergot,* 1 grain (0.065 gm.), each in a capsule, taken jointly during meals, are also very effective. The thyroid gland causes a prompt increase of fibrin ferment (adrenoxidase) and prevents the hæmorrhage, while the ergot, by inducing a rise of blood-pressure, causes the exposed area to receive an excess of blood rich in auto-antitoxin.*

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[*] *Author's conclusion.*

The deeper and greater organs, when predisposed to cancer, afford no reliable preliminary clue. Emaciation occurs when a growth is too small to give evidence of its presence, but we are no longer dealing with prophylaxis here, and the measures to be carried out are those indicated for a developed cancer, those indicated under Treatment.

Out-of-door exercise is of paramount value in the preventive treatment of cancer, to increase the vigor of the circulation in the peripheral vessels and enhance general metabolic activity. Laziness, physical and mental, predisposes to cancer, by promoting circulatory torpor and recession of the blood from the periphery.* The use of alcoholic drinks, whiskey, brandy, etc., is also pernicious, since the alcohol becomes oxidized at the expense of the blood, thus impairing its antitoxic activity.* Coffee and tea, on the other hand, are beneficial, being vasomotor stimulants.* The free use of *pure water* is in itself a protective measure, since it preserves the blood's normal fluidity.*

Such cases require watching. In one of mine, now under observation since October, 1901, a frail woman in whom the symptoms of mammary cancer were sufficiently developed to warrant operation (advised by two surgeons), the tumor was caused to recede by thyroid extract. If she allows her health to run down, however, ominous signs appear, and she must resume treatment. Arsenic is harmful in her case, a fact accounted for by the depressing influence of this agent on the adrenal system. Indeed it counteracts directly the effects of thyroid extract. An exception to the use of thyroid—or, in fact, of any drug—has asserted itself in one of my cases, *i.e.*, one of hepatic cancer. While benefited by the copious use of mineral water (Ballardvale, one quart daily) through the fact doubtless that the fluidity of the blood and of the bile facilitated the elimination of detritus, any drug, even in small doses, would at once aggravate his condition. Drugs, taken against my advice, promptly caused death. My diagnosis of hepatic cancer proved true *post mortem*.

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* *Author's conclusion.*

On the whole, the prophylaxis of cancer—which includes the prevention of recurrence after removal of the growth—entails as fundamental principle the preservation of the organism's normal defensive activity through the adrenal mechanism.*

This intimate relationship with Immunity, and which, as previously stated, I was first to point out and explain, in 1903, has since been sustained by considerable experimental evidence. Gaylord, Clowes, and Baeslack[100] found an immune body in the blood of mice which had recovered spontaneously from experimental adeno-carcinoma, while Clowes[101] afforded evidence to the effect that "mice which have recovered from cancer possess an active immunity against further inoculation." Ehrlich[102] found (1) that a rat or mouse in which inoculation had caused cancer, a second inoculation failed to do so; and (2) that when tumor material too weak to cause a growth was injected into animals, the majority of them became subsequently, *i.e.*, in from one to two weeks, immune to inoculation. To explain his first observation, Ehrlich states that the specific nutrient materials were used by the first growth—a pure supposition. From my viewpoint, the reaction of the adrenal system to destroy the tumor and its detritus, loaded the blood with antibodies, *i.e.*, auto-antitoxin, and the material of the second inoculation was promptly destroyed. Ehrlich explains his second and most valuable observation by his side-chain theory. I have shown, however, that the latter is not tenable as far as the tissue-cells being the original source of the antibodies is concerned, and that he has failed to establish the identity of these antibodies because he has neglected the ductless glands. Such obscurity does not prevail with the adrenal system as the basis of reasoning: Ehrlich produced immunity against cancer because the injected material increased powerfully the functional activity of the adrenal system, and thus caused an accumulation of auto-antitoxin of sufficient magnitude, in from one to two weeks, to protect the animal against the further inoculation—precisely as he had in his first experiment.

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* *Author's conclusion.*

[100] Gaylord, Clowes, and Baeslack: *Loc. cit.*

[101] Clowes: *Loc. cit.*

[102] Ehrlich: *Loc. cit.*

CHAPTER XXIV.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

CONVULSIVE DISEASES DUE TO HYPOACTIVITY OF THE ADRENAL SYSTEM.

A suggestive fact bearing directly upon the disorders studied in this chapter, viz., tetany, tetanus, epilepsy, puerperal eclampsia, and rabies, is that many investigators have been led to conclude by experiments in which each organ was studied individually, that the adrenals, the pituitary body and the thyroid apparatus not only influence metabolism, but that they are also concerned with the destruction of toxic waste-products. Thus, in 1891, Abelous and Langlois[1] urged that the function of the adrenals was to "neutralize or destroy toxic substances produced or elaborated during chemical interchanges, and particularly those resulting from muscular work." In 1894 Lloyd Andriezen[2] concluded that "the pituitary gland exercises a trophic action on the nerve tissues, which, in more definite terms, means enabling them" . . . . "to destroy and render innocuous the waste-products of metabolism." As to the thyroid, it may be said to have been connected with both these processes almost since any function was ascribed to this gland. "According to one hypothesis," says Howell,[3] "the function of the secretion is antitoxic. In some way it antagonizes toxic substances supposed to be formed in the body in the course of normal metabolism." We have seen in a preceding chapter, that the labors of Vassale and Generali, Gley, Moussous, Jeandelize and others have conclusively shown that this applied to the parathyroids as well.

In the first volume (1903) and in several papers written since, I pointed out that the spasmodic and convulsive phenomena witnessed after removal of either the thyroid, adrenals or pituitary should not be ascribed to the fact that absence of either of these organs prevented a direct action by their secretion or their cellular elements upon spasmogenic poisons, but that the seizures were caused by toxic waste-products, as all three of these organs formed part of the adrenal system which carried on the oxidation process through which these wastes would otherwise have been adequately catabolized. This applies also to another fruitful cause of convulsive diseases, focal infections, the most frequently met with being those of intestinal, mainly cæcal, origin.

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[1] Abelous and Langlois: Arch. de physiol. norm. et path., 5 série, vol. iv, pp. 269, 465, 1892.

[2] Andriezen: Brit. Med. Jour., Jan. 13, 1894.

[3] Howell: Trans. Congr. Amer. Phys. and Surgs., vol. iv, p. 70, 1897.

Unfortunately, confusion in respect to the pathogenesis of the group of disorders studied in this chapter still holds sway, while the appalling mortality of the acute diseases among the group continues unchecked. Of tetany, the simplest of the series, a widely read text-book of Practice still says: "The nature of the disease is unknown." Ample testimony is available to show that a corresponding ignorance of the nature of the other diseases of the group prevails. Indeed, Joseph Collins,[4] a prominent neurologist, likewise wrote: "We know very little more concerning the etiology, pathogenesis, and the clinical display of nervous diseases, organic and functional, than we did twenty years ago." This state of things will continue as long as neurologists will persist in ignoring the cardinal rôle of the internal secretions in nervous diseases.

The strength of the evidence submitted in this chapter to the effect that hypocatabolism is the underlying cause of the five diseases studied below is self-evident. Whether, as in tetany or the far more severe puerperal eclampsia, it be due to the formation of products of metabolism in excess of the quantity which the adrenal system can convert into benign and eliminable products; or to paresis of the adrenal system itself by tetanotoxin or the virus of rabies; or to functional torpor, inherited or acquired, of the same system as in epilepsy, the pathogenic agents (various intermediate products composing the poison) are the same, though the effects are greatly influenced by the degree of toxæmia, the efficiency of the test-organ, etc.

In the first volume and elsewhere I also submitted that the adrenoxin-laden plasma circulated in the axis-cylinders. Considerable evidence has since sustained this view, as we have seen. This explains, which no one had done before, the presence of tetanotoxin in the axis-cylinders and its steady progress —as well as of methylene-blue and antitoxin—in these nervous structures.

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[4] Joseph Collins: Monthly Cyclo. of Pract. Med., Feb., 1908.

Again, having urged that imperfect catabolism and inadequate functional efficiency of the adrenal system were the underlying cause of spasm and clonic convulsions, and in the presence of the striking beneficial effects of thyroid extract in experimental tetany, I laid stress on the pernicious influence of the bromides, chloral and other depressants, calling attention to the fact that, far from tending to cure, these drugs tended to kill. "They reduce, it is true," I wrote at the time,[5] "the excitability of the sensory elements, but they aid the accumulation of the spasmogenic toxics by inhibiting the oxidation process through which these are destroyed." Again, after calling attention to the hypothermia, the bromides and chloral provoked: "If the protective, curative element in these dread diseases is hyperoxidation, what may we expect of induced hypoxidation? The mortality ratio of rabies, tetanus and puerperal eclampsia treated on these lines answers that question."

Conversely, we will see in the following pages that in the *acute* diseases full doses of thyroid extract, of iodine, of the iodides, of biniodide of mercury, etc., of powerful adrenal stimulants, in a word, are curative. The paresis of the test-organ caused by the tetanotoxin and the rabic virus, and the inability of the organ to rise to the occasion in eclampsia impose the need of these large doses, the aim being to prevent the paroxysms by insuring a continuous destruction of the toxic wastes which incite them. In epilepsy, the object is the same; but small doses are alone needed here; the accumulation of toxic wastes being relatively slow, the aim is to supply the small surplus of oxygenation required, and to reduce by dietetic measures the products of metabolism formed.

On the whole, the picture submitted below of the pathogenesis of the dread diseases studied in the present chapter and the modus operandi of the various agents recommended, differ from any so far contributed except by myself. But I must again urge that with the adrenal system as the fundamental mechanism of all processes involved, the relations between cause and effect appear in their true light, viz., that it is only by aiding the body's defensive resources that we can hope to master disease.

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[5] Sajous: Jour. Amer. Med. Assoc., Feb. 4, 1905.

TETANY.

Synonyms.—*Intermittent Tetanus; Little Tetanus; Tetanilla.*

Definition.—Tetany, a disorder characterized by painful tonic spasms, is caused by waste-products which, by provoking a marked rise of blood-pressure, cause capillary hyperæmia and hyperexcitability of all organs, including the spinal and peripheral nervous systems. A spasm occurs when this general excitability is suddenly increased by the appearance in the blood of an excess of auto-antitoxin, the result, in turn, of a defensive reaction of the adrenal system, and lasts until the spasmogenic poisons have been more or less converted into harmless and eliminable end-products.*

Symptoms and Pathology.—In some cases the spasms proper are preceded by *prodromata, i.e.,* tingling or numbness of the extremities, headache, nausea and vomiting, mental depression, vertigo, irritability, a vacant stare, and transitory blindness.

The *spasms* occur in the four extremities in the majority of cases and in the upper extremities in practically all other. The thumb is flexed in the palm, the fingers are bent at the metacarpo-phalangeal joint, but stiff beyond this limit, the wrist is flexed upon the forearm and the arm folded over the chest. In rare instances, the fingers close over the thumb. The spasms soon extend to the lower extremities; as a rule, these are stiff at the hips and knees, the feet being extended and the toes flexed. The facial muscles are often involved, causing locking of the jaws, as in tetanus, and the *risus sardonicus.* When the muscles of the neck, chest and back are the seat of spasm, the head may be thrown forward or backward. and opisthotonos may occur. The diaphragm and the laryngeal muscles are not infrequently included in the morbid process, causing marked dyspnœa. Stridulous respiration and cyanosis may be provoked by the laryngospasm, a dangerous feature of this disorder. Pain in the contracted muscles and cutaneous hyperæsthesia are generally present. Among the phenomena less frequently observed are: œdema of the extremities, sweating, erythema, purpura and other eruptions, and anuria. The pulse is frequently accelerated, though the temperature is usually normal, and seldom exceeding in the exceptions 101° F. (38.3° C.).

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* *Author's definition.*

The spasms proper may last but a couple of minutes, but often they succeed one another without complete relaxation during the intervals, so that the paroxysm is in reality a series of exacerbations of spasm lasting from ten to fifteen minutes. They may recur repeatedly in twenty-four hours during several days, weeks, and even months.

Several of the phenomena mentioned do not appear in the average text-book. The vacant stare was observed by F. M. Crandall.[6] C. P. Howard,[7] in a study of a large number of cases, states that "transitory blindness has been recorded by Kussmaul, Bouveret, Trevilian and Cunningham." Of trismus, Howard writes: "That this does occur in tetany as well as in tetanus must not be forgotten, as it is present in 10 of my series," *i.e.*, 68 cases, including 9 of his own. Again, he states that "spasm of the muscles of the neck, or of the back, or of both was present in 24 cases, and in several gave rise to well-marked opisthotonos." Finally, referring to the spasm: "While usually tonic in character, it may be clonic at the onset, and in some cases from this fact may be mistaken for epilepsy; though it should be borne in mind that in true epilepsy the tonic stage always precedes the clonic. A general convulsion occurred in 13 of my series, of which 9 were children." Tetany obviously embodies many of the characteristic symptoms of tetanus and epilepsy.

Etiology and Pathogenesis.—Tetany is primarily due to an accumulation in the blood of toxic waste-products which irritate the vasomotor and sympathetic centers. The general and marked vasoconstriction which occurs, causes the blood of the large deeper vessels to be driven towards, and accumulate in, the capillaries of the entire body.[*] As the brain and spinal cord are themselves rendered hyperæmic by this process, their irritability becomes so great that the slightest excitation from the periphery evokes a violent reaction.[*] The cutaneous sensory nerve-endings being likewise rendered hyperæmic,[*] they also become hypersensitive to external impressions, and a condition is produced in which reflex spasm may be brought on by external excitants which, under normal conditions, would have produced no reaction.* Hence* the muscular contraction produced by tapping over a muscle (Chvostek's symptom), or by pressure upon a large nerve or artery (Trousseau's symptom), the marked electrical excitability (Erb's symptom) and other familiar signs.

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[*] *Author's conclusion.*

[6] F. M. Crandall: Archives of Pediatrics, Dec., 1895.

[7] C. P. Howard: Amer. Jour. Med. Sci., Feb., 1903.

That some toxic is the spasmogenic agent is now believed by practically all observers. Bouchard, Gerhardt, Bouveret and Deric,[8] Carpenter[9] and others have ascribed it to intoxication of gastric origin; Ewald and Albu[10] to a toxic alkaloid of intestinal origin found in urine; Oddo and Sarles[11] and Oddo[12] to a toxin circulating in the blood.

As to the presence of hyperæmia, Tonnelier, Blondeau, Grisolle and Trousseau recorded cases in which they had found hyperæmia of the brain and meninges, and Weiss, Bonome, Cervesato and Szabo, and others in which poliomyelitis was present. R. Peters[13] in an exhaustive analysis of 77 cases, including 7 of his own studied microscopically, found the main lesions to be a small-celled infiltration with hæmorrhages, the latter occuring preferably between the ganglia and anterior roots, inflammation of the ganglia, and pachymeningitis. Peters ascribes the disease to leucomaines or ptomaines liberated by auto-intoxication, and which exert their morbid influence upon the nerve-roots. Degenerative lesions in the gray substance and most pronounced in the anterior horns have been observed by Weiss, Bonome and others.

The frequency with which mechanical irritability of the surface occurs is shown by the fact that it was present in all of 49 cases of infantile tetany studied by Ganghofner;[14] the Trousseau phenomenon was present in 28 of these instances. Romme[15] even ascribes the laryngospasm and facial phenomena to "reflex hyperexcitability of the cord and peripheral nerves."

The manner in which the sympathetic center is influenced is considered at length under "Tetanus," a kindred disease.

Tetany occurs in the course of many diseases. Prominent among these are: (1) various gastric and intestinal disorders; (2) infectious diseases, such as typhoid fever, variola, malaria, cholera, scarlet fever, measles, erysipelas, pertussis, pleurisy, bronchitis and influenza; (3) pregnancy and lactation; (4) uræmia and insolation; (5) violent excitement and exertion. In all these conditions, tetany is an accessory phenomenon, due, not to the autotoxins or bacterial toxins they add to the blood, but to a single class of spasmogenic agent in all cases, *i.e.*, toxic products of imperfect catabolism.*

These toxic wastes accumulate in the blood, because the adrenal system—including the thyro-parathyroid apparatus—though able to supply enough auto-antitoxin and thyroidase (which as opsonin sensitizes the poison) to convert all physiological wastes into benign and eliminable end-products under normal conditions, fails to increase its functional activity sufficiently when these wastes are produced with unusual rapidity (3d, 4th and 5th group), or when exogenous poisons such as those derived from the alimentary canal, or bacterial toxins (1st and 2d group), are added to the blood.* In the former case toxic intermediate wastes simply accumulate in the blood-stream; in the latter case, the exogenous poison or toxin, by utilizing for its own neutralization a given proportion of what auto-antitoxin is available, diverts a corresponding quantity from the physiological products of catabolism, the result being the same, *i.e.*, a gradual accumulation of toxic wastes, several of which are known to be spasmogenic.*

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* *Author's conclusion.*

[8] Bouveret and Deric: Revue de méd., vol. xii, pp. 48, 97, 1892.

[9] Carpenter: Jour. Amer. Med. Assoc., Aug. 4, 1894.

[10] Ewald and Albu: "Autointoxication en des intestinal tractus," 1895.

[11] Oddo and Sarles: Marseille-médical, Oct. 1, 1894.

[12] Oddo: Revue de méd., vol. xvi, pp. 453, 573, 667, 740, 1896.

[13] R. Peters: Deut. Archiv f. klin. Med., Bd. lxxvii, S. 60, 1903.

[14] Ganghofner: Zeit. f. Heilkunde, Bd. xxiii, S. 244, 1902.

[15] Romme: Gaz. hebd. de méd. et de chir., Jan. 24, 1897.

Tetany may also be caused by (1) certain drugs, alcohol, for instance, (2) rickets and (3) removal of the thyroid and parathyroids, and myxœdema; the disorder being due here to artificially produced deficiency of auto-antitoxin and thyroidase in the blood.* Thus, alcohol becomes oxidized at the expense of the blood's adrenoxidase and so reduces the quantitative efficiency of the latter that the auto-antitoxin formed is poor in this substance; as a result waste-products are imperfectly broken down, and toxic wastes accumulate*—provided the adrenal system fails to react. Rickets, a disease due to deficient nutrition of the bones owing to tardy development of the pituitary body, *i.e.*, of the adrenal center, is self-explanatory as a cause, since the resulting deficiency of adrenoxidase entails imperfect catabolism.* Removal of the thyroid and parathyroids accounts as readily for the tetany it provokes, since it is this organ's secretion, thyroiodase* (opsonin*), which sensitizes all substances to be catabolized, besides sustaining the functional efficiency of the adrenal center up to its normal standard.*

Briefly, notwithstanding the multitude of disorders with which tetany is associated it is invariably the result of an accumulation of toxic wastes in the blood,* except when caused by exogenous poisons.

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* Author's conclusion.

Biedl[26] states that "the generally accepted view today (Pineles, von Frankl-Hochwart Chvostek) is that all forms of clinical tetany are of parathyroid origin." From my viewpoint this is due to the fact that removal or pathological destruction of the parathyroids deprives the thyroid secretion of its main antitoxic constituent.

We have seen that various authors ascribe tetany to toxins of gastro-intestinal origin. While this accounts theoretically for some cases, it fails to do so in the seven other groups enumerated, although the symptoms of the disorder are similar, though differing in intensity, in all cases. This points clearly to a common cause. The epidemic forms observed in Europe, by von Jaksch[27] and others, were in reality some obscure disorder, in the course of which tetany appeared as it does in many diseases. Tetany itself thus loses the epidemic character attributed to it by some. That several intermediate waste products capable of causing convulsions have been isolated will be shown in the articles on Tetanus and Epilepsy.

Even apart from my own views, the thyroid gland, including the parathyroids, is now regarded as serving to antagonize spasmogenic poisons. Thus Howard, referring to the investigations of Gley, Vassale, Generali, Halsted and MacCallum—all of which, beside others, have been reviewed in this work—states that "when these glands are removed, a poison which was formerly neutralized by them acts upon the central nervous system and produces tetany." MacCallum is also stated by Howard to have ascribed tetany to "the production of so much of this unknown poison that the normal parathyroids are insufficient to neutralize it." Conversely, Fleiner "regards the action of poisonous products of metabolism as of less importance than other factors," but Howard points out that "the great objection to Fleiner's theory is that it suffices only as an explanation for the gastric form of tetany." Even here it fails, for, as Howard correctly states, "Albu, Gumprecht, von Jaksch, Dickson and others have repeatedly failed to reproduce tetany by injecting into animals *untreated* gastric contents from cases of tetany." It is evident, therefore, that *not one* of the eight groups of disorders mentioned above is the spasmogenic agent, and that poisonous products of metabolism can alone be credited with this morbid rôle.

But how account for the marked clinical kinship between some cases of tetany and epilepsy? L. Pierce Clark,[28] after studying 150,000 epileptic seizures at the Sonyea Colony for Epileptics, concludes that "we must see the principle of pathogenesis in an initial toxin or auto-intoxication," *i.e.*, "an accumulation of waste-products."

When the accumulation of toxic wastes attains a certain degree which varies according to the sensitiveness of the test-organ, this organ awakens through the adrenal system a protective reaction.* The adrenals being stimulated, the proportion of adrenoxidase—and therefore auto-antitoxin—in the blood is increased temporarily.* The effect produced is apparently a morbid one, *i.e.*, a *spasm* or series of them, since the sudden increase of oxygen in the blood further excites the already hypersensitive nervous system, central and peripheral.

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* *Author's conclusion.*

[26] Biedl: "The Internal Secretory Organs," p. 46, 1912.

[27] Von Jaksch: Zeit. f. klin. Med., Bd. xvii, Suppl., S. 144, 1890.

[28] L. Pierce Clark: Med. News, July 18, 1903.

The increase of auto-antitoxin compensates for this: It neutralizes not only the toxic wastes, but also the specific poison or toxin of the disease (typhoid, erysipelas, etc.) upon which tetany, an autonomous phenomenon, may be grafted.*

The spasms of tetany are, to a certain extent, therefore, an expression of auto-protective activity.* They occur partly because the augmentation of auto-antitoxin, which is the body's main safeguard in all diseases and the active agent in all febrile processes, happens to coincide with a condition of marked irritability of the central nervous system.*

This accounts for the fact that a period of improvement often succeeds a convulsion. The curative influence of thyroid extractives or thyroid grafting in the tetany following thyroidectomy points to the manner in which the toxic wastes are neutralized. By stimulating the adrenal center the proportion of antitoxin is increased—precisely as if the thyroid gland were still present. Thus, Hutchinson[19] and others found that thyroid extract increased oxidation, while Magnus Levy[20] and Scholz[21] observed that it increased the consumption of oxygen and the proportion of CO_2 excreted. As will be shown under Treatment, it is as effective in clinical tetany as it is after thyroidectomy.

Treatment.—The primary disease, that which, by depriving the blood of some of its auto-antitoxin, renders the accumulation of toxic wastes possible, should be eliminated whenever feasible. Practically all cases in adults are due either to some gastric or gastro-intestinal disorder, or to pregnancy and lactation. Gastric dilation is not infrequently observed and it is in this class of cases that death is apt to occur. An important feature of this condition is that it is directly due to insufficiency of the adrenal system: the blood being poorly supplied with adrenoxidase, the entire muscular system is relaxed, including the musculature of the stomach.* A similar condition prevails in pregnancy, the adrenal center being unable to insure neutralization of the waste-products of both mother and fœtus.*

Under these conditions, treatment of the tetany itself (besides any other measure that the concomitant disorder demands), *i.e.*, stimulation of the adrenal mechanism to increase the blood's auto-antitoxin, meets the needs not only of the tetany, but of the primary disorder also.* Again, when we consider that it is through an increase of auto-antitoxin that all exogenous and endogenous poisons are antagonized in the blood, it becomes apparent that all agents which increase the functional activity of the adrenal system tend to cure not only tetany itself, but its cause.* *Thyroid gland* (that available, which contains parathyroid) is thus indicated in all forms of tetany. Large doses have been found necessary; 5 grains (0.3 gm.) or more every three hours may be used at first, and gradually increased. *Parathyroid* is beneficial in some cases, but probably only the milder ones. (See also p. 741, vol. i.)

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* *Author's conclusion.*

[19] Hutchinson: Brit. Med. Jour., July 16, 1898.

[20] Magnus Levy: Berl. klin. Woch., Bd. xxxii, S. 650, 1895.

[21] Scholz: Cent. f. inn. Med., Bd. xvi, S. 1041, 1069, 1895.

It is probable that the underlying cause of tetany in many cases is deficiency of thyroid secretion. Thus Gottstein[32] arrested tetany of twenty years' duration in a case of myxœdema. Yung, Breisach, Murray, Hutinel, Maestro[33] and Byrom Bramwell[34] have also reported cases of tetany or laryngospasm apparently devoid of hypothyroidia benefitted and even cured by thyroid extract.[35] Levy-Dorn[36] obtained striking results in a case following parturition, the spasm ceasing after the sixth dose. Other instances of this kind have been reported. This result obtains, however, only in cases in which the adrenal center responds to excitation; it may be too poorly developed to do so, as in some rachitic children, or it may have been so actively stimulated by the concomitant process, pregnancy for instance, that its efficiency cannot be raised further even by thyroid extract and the tetany persist.

As to the value of parathyroid extract, the question is still unsettled. Easterbrook[37] tried parathyroid extract in several cases, employing enormous doses in some; the only effect was a slight rise of blood-tension. MacCallum,[38] however, was able to arrest the symptoms produced by excision of the parathyroids by injecting the blood of a normal dog. The same observer and Davidson[39] found that an emulsion or extract, to produce its maximum effect, must be introduced into the veins in considerable quantity—a fact which they think tends to militate against its use in human beings, although it might be of use in cases due to partial adrenal insufficiency. This is sustained by the observation of Loewenthal and Wiebrecht that it was beneficial in some cases and not in others. The fact that the product of the parathyroids is but a constituent of thyroidase probably accounts for its relative inertness. In the light of my views it requires the secretion of the thyroid to acquire its physiological power.

In children gastro-intestinal disorders are likewise the primary exciting cause in the majority of cases. Purgation and attention to the diet sometimes suffice to arrest the spasms. *Thyroid gland* has also given good results in such cases after the alimentary canal had been judiciously treated. *Calomel,* which also stimulates energetically the adrenal center,* has been used advantageously every other day in $^3/_4$ grain (0.05 gm.) doses to prevent the formation of toxic substances.* *Saline aperients* are also useful in such cases. *Salol,* 5 grains (0.3 gm.), has been recommended for the same purpose. *Warm baths,* by drawing blood to the periphery and increasing (owing to the heat, which enhances the energy of all ferments) the proteolytic activity of its auto-antitoxin,* are very beneficial.

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* *Author's conclusion.*

[32] Gottstein: Deut. Zeit. f. Nerven., Bd. vi, S. 177, 1895.

[33] Maestro: Rif. Med., vol. xii, Pt. ii, p. [illegible], 1896.

[34] Byrom Bramwell: Brit. Med. Jour., June 1, 1895.

[35] Cited by Jeandelize: "Insuffisance thyroïdienne, etc.," 1902.

[36] Levy-Dorn: Therap. Monats., Bd. x, S. 63, 1896.

[37] Easterbrook: Lancet, Aug. 6, 1898.

[38] MacCallum: Med. News, Oct. 31, 1903.

[39] MacCallum and Davidson: *Ibid.*, Apr. 8, 1905.

Oddo[illegible] found calomel very efficacious in the above dose, for the expulsion of intestinal toxic substances and their removal. With Hauser[illegible] he recommended lavage, but this is a difficult and dangerous procedure in tetanic children. Maestro observed that thyroid gland, administered raw or slightly cooked, 30 to 60 grains (2 to 4 gms.) daily, to children, rapidly diminished the intensity of the spasms and finally arrested them. Warm baths are recommended by many clinicians; the efficiency of ferments being raised by heat, the trypsin of the auto-antitoxin acquires increased activity; moreover, the congestion of the central nervous system is markedly relieved.

Saline solution is a useful adjuvant to increase the osmotic properties of the blood and thus facilitate the circulation of the auto-antitoxin.* It may be given orally in adults and by enema in children, large quantities being injected.

Kussmaul long ago suggested that the spasms were at least partly due to diminution of the body fluids—the theory of "dehydration" supported by other clinicians. It is mainly in severe types of tetany that the decinormal solution is effectual. Thus Gomes[illegible] obtained prompt results and finally recovery in cases in which the spasms included opisthotonos.

To control the spasms, 10-grain (0.65 gm.) doses of *bromide of sodium* usually suffice; such doses reduce the excitability of the vasomotor and sympathetic center just enough to diminish the cutaneous congestion without lowering the activity of the adrenal center.* If it fails to reduce the spasm *chloral hydrate* may be added to the bromide, also in 10-grain doses. In children the chloral may be given by enema. Additional measures to relieve the spasm are given in the article on Tetanus.

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* *Author's conclusion.*
[illegible] Oddo: *Loc. cit.*
[illegible] Hauser: Berl. klin. Woch., Bd. xxxiii, S. 782, 1896.
[illegible] Gomes: Rif. Med., vol. xvi, Pt. i, p. 297, 1900.

TETANUS.

Synonym.—*Lockjaw.*

Definition.—Tetanus, a condition characterized by paroxysms of severe tonic spasm, is the terminal stage of an infection by a specific bacillus the toxin of which causes paresis of the test-organ. The functions of the adrenal system being inhibited, toxic waste-products accumulate in the blood which provoke an intense rise of blood-pressure and, as a result, capillary hyperæmia and hyperexcitability of all organs, including the spinal and peripheral nervous systems. A spasm occurs when this hyperexcitability is suddenly increased by the appearance in the blood of an excess of auto-antitoxin, the result, in turn, of a defensive reaction of the adrenal system, and lasts until both the specific toxin and the toxic wastes have been more or less converted into harmless and eliminable end-products.*

Symptoms and Pathology.—The tetanic paroxysms appear from a few hours to two weeks after the introduction of the specific agent of tetanus into the tissues. The attack is sometimes preceded by chilly sensations, hypothermia, lassitude, yawning, and in traumatic cases by some tenderness and muscular twitchings in the neighborhood of the wound.

The attack itself begins by more or less marked rigidity and perhaps slight pain of the muscles of the jaws, neck, tongue and œsophagus, the patient soon finding it difficult to swallow and then impossible to open his mouth. This stiffness gradually invades the entire body, *i.e.*, the muscles of the back, abdomen and legs, and the patient finally becomes as stiff as a board. In some cases the spasm occurs in certain groups of muscles earlier than in others and the body may be bent to one side or the other, backward—opisthotonos—or forward. The facial muscles may also contract irregularly, causing distortion of the features; the eyebrows may be raised and the angles of the mouth elevated, causing the grin of tetanus, *i.e.*, the *risus sardonicus.* The paroxysms, at first comparatively painless, become extremely severe, the patient being often in drenching sweat; but fortunately they do not generally last longer than fifteen seconds. They may be provoked by the slightest touch, a breath of air, noise, etc.

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* *Author's definition.*

When the muscles of respiration and the diaphragm take a very active part in the spasm, the respiration becomes hurried and short and the patient may die of asphyxia. The heart may likewise be inhibited through excessive constriction of the coronaries,* and its action become very weak, irregular and finally arrested. Although the temperature may rise moderately during the seizure, it sometimes becomes high—110° F. (43.3° C.) on the approach of death. Most cases die within the first few days, but some may endure much longer—weeks even.

Pathogenesis.—Tetanus is due to the accumulation in the blood of certain poisons which cause marked irritation of the sympathetic and vasomotor centers.* The propulsive activity of the arterioles is not only enhanced to a marked degree by the exaggerated sympathetic impulses, but the irritation of the vasomotor center, by provoking excessive and general vasoconstriction, causes the deeper vascular trunks to drive a part of their blood into the peripheral capillaries, including those of the spinal cord and skin.* The spinal reflex centers being thus rendered excessively irritable and the cutaneous sensory terminals correspondingly sensitive, a condition is produced in which a spasm may be brought on at any moment by the slightest exciting cause, a touch, a breath of air, a slight noise, etc., or some endogenous excitant.*

The blood-pressure was found elevated by Tauber[53] not only during spasms, but also during the intervals. The arterial tension is so great in some cases that rupture of the capillaries may be caused by the blood forced into them. Thus, Molle[54] observed hæmorrhage in tetanus. Marinesco[55] found diffuse hæmorrhages in the gray substance of the spinal cord, especially in the anterior horns. Hunter[56] noted marked dilation of the spinal vessels, coupled with infiltration and miliary hæmorrhages; Matthes[57] also found in the spinal cord extensive hæmorrhages and disseminated smaller hæmorrhages, coupled with "enormous" enlargement of all the small blood-vessels—a condition which the author ascribes to hyperæmia, and not to the tetanus poison. Of course, all muscles, including those of the vessels, being abnormally contracted during spasm, the blood-pressure is higher during the latter than during the intervals, but the fact remains that the blood-pressure is high during the entire course of the disease and that this is due to irritation of the spinal cells.

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* *Author's conclusion.*

[53] Tauber: Wiener klin. Woch., Bd. xi, S. 747, 1898.

[54] Molle: Bull. méd., vol. x, p. 135, 1896.

[55] Marinesco: C. r. Soc. de biol., 10 série, vol. iii, p. 726, 1896.

[56] Hunter: Brit. Med. Jour., Aug. 7, 1897.

[57] Matthes: Deut. Zeit. f. Nerv., Bd. xiii, S. 464, 1898.

As to the participation of the sympathetic center in the process, we have seen that Cyon produced spasm by exciting this organ, *i.e.*, the seat of the general sympathetic center, as I have pointed out. These fibers, after leaving the pituitary and the nucleus above, pass posteriorly along the walls of the third ventricle. This accounts for the muscular movements noted by Flourens, Bechterew, Weber, Ferrier and others on exciting the walls of the third ventricle. Ziehen,[38] moreover, found that removal of the hemispheres in rabbits and excitation of the remaining structures, including the corpora quadrigemina, caused prolonged tonic spasm. Prus[39] then found that when the pyramids had been divided, the spasmogenic impulses passed by way of the base, *e.g.*, the tegmentum and pons, an observation confirmed by Bischoff,[40] Hering and others.

Hering,[41] in experiments which included twenty monkeys, ascertained that after division of the pyramids in the latter animal it was impossible "to inhibit a tonic spasm in the isolated extremity." In an extensive series of experiments, Nino Samaja[42] recently showed, in fact, that in the higher mammals *tonic* convulsions were "exclusively" due to impulses from the *base* of the brain, the path, we have seen, of the sympathetic filaments derived from the pituitary body.

The presence of marked hyperæmia of the spinal system is generally recognized. Thus Ewing,[43] referring to the spinal cord of a case examined by him, states that "the capillaries were everywhere distended with blood and a few minute extravasations were found in the floor of the fourth ventricle."

When the accumulation of toxic wastes in the blood exceeds a certain limit, the test-organ incites a protective reaction through the adreno-thyroid center.* A large quantity of auto-antitoxin suddenly invading the blood, the existing hypersensitiveness of all nervous elements, central and peripheral, is increased, owing to the increased rapidity of metabolism, and a spasm occurs.* Indeed, the spasms should not be regarded as constituting the disease as the term "tetanus" suggests; they represent a *terminal phase of the disease,* when the accumulation of poisons in the blood has become so great that a supreme physiological effort is necessary to destroy them.* Each spasm represents such an exacerbation of protective activity.*

The increase of auto-antitoxin in the blood being itself paroxysmal, as in all convulsive disorders, the erethism and sensibility of the spinal and cutaneous nerve-cells are also paroxysmal. Yet the paroxysm is not due to direct excitation, by the auto-antitoxin, of the cerebro-spinal cellular elements; these are merely rendered still more irritable than before.* The true spasmogenic factor is the skin, owing to the presence therein of the sensory nerve-endings, which, more easily than other nerve-elements, are capable of provoking reflex motor spasm. In other words, the wave of auto-antitoxin acts as an endogenous excitant, much as would one of the exogenous excitants, a touch, a noise, etc., on the surface, and a reflex spasm follows.*

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* *Author's conclusion.*

[38] Ziehen: Deut. med. Woch., Bd. xiv, S. 604, 1888.

[39] Prus: Wien. klin. Woch., Bd. xi, S. 857, 1898.

[40] Bischoff: *Ibid.*, Bd. xii, S. 960, 1899.

[41] Hering: *Ibid.*, Bd. xii, S. 831, 1899.

[42] Nino Samaja: Rev. méd. de la Suisse rom., Mar. 20, 1904.

[43] Ewing: Arch. of Neur. and Psych., vol. i, p. 263, 1898.

The accumulation of adrenoxidase and the resulting rise of temperature vary considerably in different cases, the adrenal center being sometimes unable to react with sufficient vigor to master the situation. D'Arsonval[44] not only observed in some experimental animals a rise of 40° to 41° C. (104° to 105.8° F.) and above, but he states that the spasms "correspond exactly with the *hyper*productions in the thermogenesis." This clearly shows that while a continuous febrile process was present, the spasms coincided with the exacerbations of that process, in accord with my conclusions. Indeed, Thaon[45] recently found clear signs of overactivity of the pituitary after death from tetanus.

The fundamental experiment of Hales, that suppression of the cord in frogs prevented all reflex response always obtained on irritating the skin, is complemented by the well-known fact that the application of cocaine to the skin prevents the convulsion of strychnine. Courmont and Doyon,[46] working in the laboratories of Arloing and Morat, pointed out, after exhaustive experiments in frogs, guinea-pigs, rabbits and dogs, that the spasms of tetanus were also reflex and produced by irritation of the peripheral sensitive nerve-endings—a view sustained experimentally by Brunner[47] and others. Moreover, Courmont and Doyon adduced considerable testimony showing that the supposed tetanic poison was not such and that a chemical phase existed between this poison and the spasm. Though they failed to discern the identity of this intermediate substance, their[48] experiments imposed the conclusion that they were "newly formed in the body" as shown below.

Etiology.—The primary cause of the disease in *traumatic tetanus* is the presence in the tissues of the tetanus bacillus, found in the soil and in the pus of wounds of individuals suffering from the disease. It occurs mainly in garden soil containing manure, in the superficial dirt of streets, roads, stables, etc., and enters the tissues when these are lacerated—even though the injury be slight—with what soil penetrates the wound. An injury of the hands when they are soiled may thus initiate tetanus, while a sharp object such as a nail, a piece of glass, etc., which has lain in the dirt, on penetrating the foot may also introduce therein the pathogenic germ. It may likewise be introduced during vaccination, the surgical use of gelatin, etc.

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* *Author's conclusion.*

[44] D'Arsonval and Charrin: Arch. de physiol. norm. et path., T. x, p. 740, 1898.

[45] Thaon: Thèse de Paris, 1907.

[46] Courmont and Doyon: C. r. Soc. de biol., 9 série, vol. v, p. 618, 1893; Arch. de physiol. norm. et path., 5 série, vol. v, pp. 64, 114, 1893.

[47] Brunner: Arch. russes de pathol., Mar. 31, 1896.

[48] Courmont and Doyon: Arch. de physiol. norm. et path., T. ix, p. 716, 1897.

Tetanus neonatorum, which ensues when the umbilical cord is not properly cared for, the tetanus following vaccination and injection of antitoxin, in surgical operations, etc., are all caused by the bacillus tetani.

Idiopathic tetanus is also ascribed to the tetanus bacillus, which is thought to penetrate the skin or mucous membrane by some undiscovered injury. As it has been found in large quantities in the fæces, it is thought to be a host of the tissues, though not of the blood itself, and to multiply when exposure to cold, and other conditions which lower the resistance of the tissues, favor its multiplication.

The bacteriology of idiopathic tetanus is still very obscure. Yet in the light of my views, cold, exposure, etc., may well facilitate the multiplication of germs present in the tissues. Thus, Pizzini[illegible] found the bacillus tetani in the fæces of stable attendants. Leucocytes being, as we have seen, the intermediaries between the intestinal canal and the tissues, the manner in which the germs may be transported to the latter is obvious.* As cold inhibits proteolytic activity by lowering the temperature of the ferment, the digestive activity of the leucocytes may itself be impaired and the—extremely resistant—tetanus bacilli reach the tissues unharmed and quite able to multiply.*

Once in the tissues, the bacillus remains at the seat of infection and multiplies *in situ*. Here it secretes a very poisonous toxin, which increases in quantity gradually as the multiplication of the germ progresses, and the time finally arrives when the blood contains a sufficient amount to initiate the terminal phase of the infection, *i.e.*, tetanus.

The toxin of the tetanus bacillus is not, as now believed, the direct cause of the spasms witnessed during the disease.*

Considerable importance is now attached to the presence of the toxin in the nerves themselves, besides that found in the blood, a fact demonstrated by Bruschettini, in 1892, and confirmed by Marie[illegible] and others. Since I have shown,[illegible] however, that the blood-plasma circulates in the nerves, *i.e.*, in the axis-cylinders, the presence of toxin in them becomes a normal phenomenon. As Gumprecht found it also in the neural lymphatics, it evidently enters likewise the tissue lymphatics and may thence be readily carried to the blood-stream and penetrate the nerves. Marie and Morax,[illegible] in fact, after injecting a tenfold fatal dose in the leg-muscles of guinea-pigs, found the toxin in the blood and sciatic nerve of the corresponding side. They ascertained also that the axis-cylinders took up the toxin centripetally—the direction taken by the blood-plasma. Meyer and Ransom[illegible] confirmed these observations.

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* *Author's conclusion.*

[illegible] Pizzini: Rev. d'ig. e san. pub., No. 5, 1896.

[illegible] Marie: Ann. de l'Inst. Pasteur, vol. xi, p. 591, 1897.

[illegible] *Cf.* vol. i, pp. 532 *et seq.*, and also this vol., chapter fifteenth.

[illegible] Marie and Morax: Ann. de l'Inst. Pasteur, vol. xvi, p. 818, 1902.

[illegible] Meyer and Ransom: Proceedings Royal Soc., vol. lxxii, p. 26, 1903.

As interpreted from my standpoint, these phenomena merely exemplify the manner in which any poison enters the neural elements with the plasma. Indeed, we have seen that Meltzer showed that methylene-blue entered the axis-cylinders at either end.

That the toxin of the bacillus tetani is not the direct cause of the spasms of the *disease* is shown in various ways. (1) When injected into nerves, as observed by several investigators, it evokes spasm of the corresponding extremity or region supplied by that nerve or by the special cells reached by the poison. This is not the case in tetanus; while the muscles around the wound may be somewhat spastic, the spasms of tetanus begin in the face or neck (hence the term "lockjaw"), even though the source of the toxin, the injury, be in the foot—anywhere, in fact. (2) Meyer and Ransom found that when introduced directly into the posterior root of a spinal nerve between the posterior ganglion and the cord, the toxin caused excruciating pain. In tetanus no such pain appears, notwithstanding the predilection of the toxin for the spinal gray substance. (3) As observed by Courmont and Doyon, a certain dose is fatal to an animal after a period of incubation; this dose may be increased to any extent, one hundred fold, even, without shortening this period. In the case of true spasmogenic poison, strychnine, for instance, the larger the dose, the sooner death occurs. (4) Meyer and Ransom found that when the toxin was injected in a vein, a period of incubation of three or four days was followed by true tetanus. Why this delay, if the toxin produces spasms by acting directly on the nerve-cells? It cannot be ascribed logically to delay in reaching the central system, since a sufficient dose of strychnine introduced in the same way produces spasm in a few minutes. This is further emphasized by the fact that the lethal activity of tetanus toxin according to Lehmann and Neumann[44] is from 30 to 100 times greater than that of strychnine.

The first effect of the soluble toxin is to stimulate the test-organ, *i.e.*, the adrenal center—an auto-protective reaction.* As a result, there occurs an abundant production of adrenoxidase, and therefore of auto-antitoxin in the blood,* and, in robust individuals, moreover, a marked leucocytosis. The success of the immunizing process depends upon the efficiency of this auto-protective function,* and to some extent upon the quantity of infectious material introduced. It is probable that most wounds in which soil has penetrated are contaminated, and that the great majority are not followed by tetanus only because the antitoxic and phagocytic properties of the blood can successfully cope with the bacilli and their toxins from the outset.*

Courmont and Doyon, we have seen, concluded after many experiments that tetanus was caused by soluble substances "newly formed in the body," under the influence of the toxin. Though unable to indicate their source or identity, they also found that when a dose of extract of tissues containing tetanus toxin (extract of normal tissues giving no result) too small to cause death was injected into an animal, its blood soon contained "in abundance" a spasmogenic soluble substance. Of this substance, they say: "It *resists prolonged boiling*, although the products of the bacillus become inactive above a temperature of 65° C." These results have been confirmed by Buschke and Oergel[55] and by Blumenthal.[56] Now, we have repeatedly seen that oxidase alone stands boiling without being destroyed, and that it can itself provoke tetany by enhancing excessively the energizing properties of the blood and the irritability of nervous elements, peripheral and central. It is plain, therefore, that tetanus toxin can, in small doses, powerfully stimulate the adrenal center, *i.e.*, the auto-protective functions of the body.

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* *Author's conclusion.*

[44] Lehmann and Neumann: "Bacteriology," American edition, by Weaver, p. 78, 1901.

The phagocytic properties of the blood are also greatly increased, and Metchnikoff, Vaillard and Vincent[57] and others have shown that, under favorable conditions, phagocytosis sufficed to arrest the morbid process.

When the protective resources—phagocytes and auto-antitoxin—of the body are unable to destroy the pathogenic germs and their products as fast as they increase in the blood, the toxin depresses and tends to paralyze the functional efficiency of the adrenal center.* By thus inhibiting the formation of adrenoxidase, and therefore of auto-antitoxin, the toxin prevents the destruction of physiological wastes which include several intermediate toxic bodies.*

Striking, in this connection, is the testimony of physiological chemistry. Oxidase, we have seen, is a soluble globulin mixed with the blood's serum albumin. Chittenden,[58] referring to the tetanus that follows thyroidectomy in animals, says that "in the period *preceding* the convulsions the precentage amount of serum albumin is increased and the *globulins decreased.*" Now, the symptoms of the period of incubation, chilliness, actual rigors and hypothermia, yawning, lassitude, etc., clearly point to the time when, overwhelmed by the accumulated toxins, the adrenal center is losing ground and reducing passively, therefore, the oxidase supplied to the blood. Injected toxin sometimes evokes nothing but such symptoms, causing extreme hypothermia and death, as observed by Binot.[59] Dönitz[60] also obtained, by large doses in susceptible animals, great wasting with occasional convulsions and finally general paralysis. Montesano and Montessori[61] found active tetanus bacilli in the cerebro-spinal fluid of a case of general paralysis. Cases of paralysis of facial muscles have also been observed by Rose, Lépine, Waltenhoff,[62] J. Hendrie Lloyd[63] and others—a fact which suggests that the tetanus toxin may not limit its paralyzing action to the adrenal center. Federoff[64] likens the virulence of the toxin to that of snake-venom. As in the case of the latter, the blood is sometimes laked—evidence, we have seen, of advanced adrenal insufficiency.

The toxic wastes that remain undestroyed in the blood soon begin to accumulate therein, and constitute the true intrinsic pathogenic agents of the disease, since they are the irritants which cause the vasomotor and sympathetic centers to become hypersensitive in the manner defined under the preceding heading.*

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* *Author's conclusion.*

[55] Buschke and Oergel: Deut. med. Woch., Bd. xix, S. 149, 1893.

[56] Blumenthal: Zeit. f. klin. Med., Bd. xxxii, S. 325, 1897.

[57] Vaillard and Vincent: Ann. de l'Inst. Pasteur, vol. v, p. 1, 1891.

[58] Chittenden: Trans. Congr. Amer. Phys. and Surg., vol. iv, p. 92, 1897.

[59] Binot: Gaz. hebd. de méd. et de chir., July 30, 1899.

[60] Dönitz: Deut. med. Woch., Bd. xxiii, S. 428, 1897.

[61] Montesano and Montessori: Centralbl. f. Bakt., Bd. xxii, p. 663, 1897.

[62] Cited by Worms: Thèse de Lyon, 1905.

[63] J. Hendrie Lloyd: Jour. Amer. Med. Assoc., Oct. 7, 1905.

[64] Federoff: Thèse de Moscow, 1896.

As tetanic spasms always occur (in carnivora) after experimental thyroidectomy, they cannot be ascribed to the tetanic toxin, or to poison of external origin. Some toxic substance formed in the body itself can alone, therefore, be accountable for the intense irritability of the spinal cells which renders the occurrence of seizures possible under the least excitation, extrinsic or intrinsic. The prevailing view at the present time is that of Victor Horsley,[65] Blumreich and Jacoby[66] and others, *i.e.*, that the spasms are due to "one or more toxic substances tending to accumulate in the blood" (Schäfer[67]). Referring to the tetanus of experimental thyroidectomy, Chittenden[68] also says: "It would appear that in the first stages is an abatement of the metabolism of the tissues, followed by an increase, and that possibly in the incomplete breaking down of the proteid material, *intermediate toxic products* appear which are the *cause of the cachexia.*"

Prophylactic Treatment.—Notwithstanding the hopeful outlook once afforded by the serum or "antitoxin" treatment, it has signally failed to influence the mortality of developed cases of tetanus, *i.e., about 80 per cent.,* while that of the 4th of July tetanus, the toy pistol, fire-crackers, etc., is 95 per cent. As a prophylactic, however, antitoxin is of undoubted value. The highest mortality occurs within the first seven days after the onset of the convulsions; after this the chances of recovery increase in proportion with the duration of the disease.

In their study of the reports of 1201 cases, Anders and Morgan[69] state that "as a means of prophylaxis the serum has been fully tested both in America and abroad," and there is "uniform agreement that 'antitoxin does protect' in every case." They also conclude, however, that "on the other hand, the present status of the serum question leaves no room for doubting that when given during a well-developed case of tetanus, antitoxin does not have any appreciable beneficial effect, neither the mortality being reduced nor recovery hastened thereby." In the 870 cases in which the duration of the disease had been given in the report, the highest mortality occurred on the seventh day. From the tenth day gradually, and the fifteenth rapidly, the mortality decreased. Jacobson and Pease,[70] after a comprehensive study of reported cases, conclude that "as a prophylatic measure it merits our fullest confidence."

The undiminished mortality of tetanus notwithstanding all the work done in recent years emphasizes the great importance of surgical prophylactic measures. All injuries in which contamination is probable should at once be carefully asepticized, opening freely under anæsthesia if required, until all tissues reached by the destructive agent, and all local detritus, foreign bodies, necrosed tissue, etc., are brought to view. The edges of the wound should be retracted and all tissues exposed to the air (the tetanus bacillus being killed by oxygen) and finally washed out with *hydrogen peroxide* injected into every recess of the wound. The next procedure is to apply a thick layer of *antitetanic serum* to the thoroughly disinfected surfaces, preferably in the form of powder of the dried serum. The wound should then be dressed. Complete but loose *iodoform* gauze packing—thus permitting the access of air to the tissues and free drainage—has given the best results.

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* *Author's conclusion.*

[65] Victor Horsley: Proc. Royal Soc. of London, vol. xl, p. 6, 1886.

[66] Blumreich and Jacoby: Arch. f. d. ges. Physiol., Bd. lxiv, S. 1, 1896.

[67] Schäfer: "T. B. of Physiol.," vol. i, p. 942, 1898.

[68] Chittenden: Trans. Congress Amer. Phys. and Surgs., vol. iv, p. 93, 1897.

[69] Anders and Morgan: Jour. Amer. Med. Assoc., July 29, 1905.

[70] Jacobson and Pease: Annals of Surgery, Sept., 1905.

J. Alison Hawkes, of Melbourne,[71] found hydrogen peroxide of value in a case in which the seizures had already developed. The powerful oxidizing properties of this agent render it invaluable in this connection. The local use of powdered antitoxin is considered by Letulle[72] a positive preventive. Calmette and also McFarland[73] observed that though not absorbed from the skin or mucous membranes, antitetanic serum, even when dried, was promptly absorbed by denuded surfaces, wounds, etc., and conferred immunity on animals. Cauterization of the wound should be avoided; the eschars tend to close it, and thus to provide the tetanus bacillus the environment it requires to pullulate, *i.e.*, one deprived of oxygen.

Agents Which Increase the Bactericidal and Antitoxic Properties of the Blood.—The marked prophylactic value of *antitetanic serum* is due to the fact that it increases the relative proportion of auto-antitoxin, from which, as I have shown, it does not differ in general composition. Its action is the same on the bacteria, their spores and their toxins. As soon as the wound is dressed, therefore, at least 10 c.c. ($2^1/_2$ drachms) of American serum should be injected into a vein. An equal quantity should then be injected each day. When the injury is extensive, or if considerable laceration of tissue have occurred, the dose should be larger.

The now established value of antitetanic serum as a prophylactic sustains the remarkable results obtained by Nocard,[74] who administered two injections of antitetanic serum to each of 2707 horses, after such operations as castration and docking, and to 2300 and then again to 400, one to four days after accidental wounds and injuries. One only had a slight attack of tetanus, from which it soon recovered. The district was one in which tetanus was very rife, and in the same period 259 other horses, many of them from the same stables as those that he thus immunized, died from this cause.

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[71] J. Alison Hawkes: Brit. Med. Jour., Apr. 18, 1896.
[72] Letulle: Presse méd., vol. xi, p. 453, 1904.
[73] McFarland: Jour. Amer. Med. Assoc., July 4, 1903.
[74] Nocard: Semaine méd., vol. xvii, pp. 272, 286, 1897.

As *thyroid gland,* as shown below, promptly arrests the tetanus that follows removal of the thyroid, and this form being similar to the typical tetanus, it is indicated in the latter, in 5-grain (0.3 gm.) doses three times daily in adults, as a prophylactic.* It stimulates powerfully the adrenal center and therefore increases correspondingly the proportion of adrenoxidase in the blood.* But it is only as a prophylactic that it can be given in full doses.

All agents which stimulate the adrenal center, though inferior to thyroid extract, are capable of augmenting the antitoxic properties of the blood and cannot, therefore, but be of value as prophylactics.* The *iodides* produce effects similar to those of thyroid extract, but less rapidly; at least 10 grains (0.64 gm.) should be given three times daily to adults, to evoke rapidly its physiological effects.* *Biniodide of mercury,* ¼ grain (0.016 gm.), three times daily, closely watched to avoid salivation, also powerfully stimulates the adrenal center.* Other agents of the same class, referred to below, are also endowed with properties which render them suitable as prophylactic agents.

Treatment of Developed Tetanus.—Once the disease has reached the last stage, *i.e.*, that attended with spasm,* antitetanic serum, we have seen, does not influence favorably its lethal tendency. The main reason for this is that the amount introduced in the blood, even in the largest doses, is often inadequate to compensate for the deficiency of adrenoxidase and, therefore, of auto-antitoxin, which the depressed condition of the adrenal center entails.* The spurts of activity of which this center is the seat* are sometimes sufficiently violent, even under these conditions, to overcome the toxæmia, but the mortality ratio shows that in the great majority of cases this result is not attained. The aim, therefore, should be to supplement the action of the antitetanic serum by that of auto-antitoxin; this may be done by the simultaneous use of *thyroid*

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* *Author's conclusion.*

gland in full doses, adjusted, as stated below, to the needs of the auto-protective process.* It is capable alone, in fact, of arresting tetanic convulsions.

The tetany that follows thyroidectomy often assumes the character of true tetanus. Even when the disease is well advanced, the spasms may be promptly arrested with thyroid extract, as shown by Vassale[75] and Gley[76] and many other investigators since, as is well known. This applies likewise to the active organic principle of the thyroid, iodothyrin. Thus, Hofmeister[77] found that iodothyrin cuts short the symptoms that follow removal of the thyroid, including the convulsions. Baumann and Goldmann[78] showed, moreover, that thyroidectomized dogs do not suffer from tetanic convulsions so long as adequate doses of iodothyrin are administered, and that they recur when the iodothyrin is withdrawn.

The introduction of the *antitetanic serum* into the nerves, the spinal cord or the brain, tends to induce shock and further to depress the adrenal center; and as, on the whole, such severe procedures have not lowered the general mortality of tetanus, they are not recommended.* Conversely, as the antitetanic serum, on entering the blood-plasma, circulates with the latter in the axis-cylinders, its intravenous use insures its penetration to all the irritable nerve-elements, central and peripheral, with far more certainty than do the above-mentioned procedures, which tend to localize its action.* Not less than 10 c.c. (2$^1/_2$ drachms) of the serum should be injected at a time, preferably into the median basilic vein; and, in order to sustain its action, this dose should be repeated every three hours. If the temperature is but little above normal, which indicates that the auto-protective processes are inadequate,* larger doses should be given.

Loeper and Oppenheim,[79] in a study of 208 cases, including 5 of their own, 59 of which were treated by the intracerebral method and 144 by intravenous or hypodermic injections, found the mortality greater in the former, even in cases of equal severity; they concluded moreover, that the intracerebral injections were not devoid of danger. Gibb[80] reported a case in which it caused a fatal cerebral abscess. Meyer and Ransom regard intraspinal injections as of no greater value than the intravenous or hypodermic method, while the anatomical relations are such, as shown by Browning,[81] that there is but little absorption by the spinal cord proper from the subarachnoid space. On the other hand, in the intravenous method, the serum is first taken to the heart, and in less than 30 seconds is distributed everywhere. Very large doses may safely be injected in this manner (avoiding the introduction of air): Kocher,[52] for instance, injects 50 c.c. (13½ drachms) at a time in the median basilic vein. Doubtless many cases are lost because too little serum is supplied to the blood to enable it to cope with the disease. Elting[53] injected 350 c.c. (nearly 13 ounces) in 24 hours in a case which terminated favorably. Rosa Engelmann[54] holds that the ineffectiveness reported is due to insufficient doses. As my analysis of its composition shows, it is quite harmless, notwithstanding its marked antitoxic power.

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* *Author's conclusion.*

[75] Vassale: Rivista sperimentale di fren., vol. xvi, p. 439, 1890.

[76] Gley: C. r. de la Soc. de biol., vol. iii, 9 série, p. 843, 1891.

[77] Hofmeister: Deut. med. Woch., Bd. xxii, S. 341, 1896.

[78] Baumann and Goldmann: Münch. med. Woch., Bd. xliii, S. 1153, 1896.

[79] Loeper and Oppenheim: Arch. gén. de méd., vol. clxxxv, p. 426, 1900.

[80] Gibb: Brit. Med. Jour., July 1, 1899.

[81] Browning: "Circulation in the Central Nervous System," 1897.

The *supplemental* use of *thyroid gland* is indicated when, notwithstanding the intravenous injection of large doses of serum, the temperature remains comparatively low. A dose varying from 5 to 10 grains (0.3 to 0.64 gm.)—the lower the temperature the larger the dose—may be given every three hours at first.* After a couple of doses, the temperature should begin to rise.* In this event, the effects should be carefully watched, since the increased metabolic activity engendered by the thyroid may, we have seen, increase the number of convulsions, when either of the measures indicated below to control the latter should be resorted to. Should the temperature not rise, the thyroid gland should be given steadily, the dose and its continuance being regulated according to the effect produced.* If antitoxin cannot be obtained, thyroid gland is capable of replacing it by administering large doses at short intervals.*

Experiments have shown, as is well known, that when injected soon after infection with many times the lethal dose, antitoxin will save the poisoned animal. As the time elapsed since infection increases, however, larger doses are required to do so, until a time is reached when antitoxin will lose its effect entirely. It is in such cases that the temperature will not rise.* Thus Möllers[55] used large doses in four cases within 30 hours after the first symptoms of tetanus had appeared; yet all died. He specifies, however, that all were free from fever. Conversely, Anders and Morgan, in the statistical paper already referred to, write: "Hyperpyrexia was noted in two cases of our series; this is supposed to be an ominous sign, but both instances ended in recovery." In a case reported by Leyden[56] the temperature, 105.8° F. (41°C.), fell soon after giving antitoxin, and the case steadily improved. It is precisely this curative process that thyroid extract evokes in experimental animals. Thus, as emphasized by Hutchinson[57] and others, all the systemic oxidation processes are increased by the use of thyroid extractives. Magnus Levy[58] and Scholz[59] found that they increased the consumption of oxygen and the proportion of carbonic acid excreted. Waste-products of metabolism being, as we have seen, the direct irritant of the central nerve-cells, and the cause of the convulsions, they are evidently destroyed —along with the tetanus bacillus and their toxin—since Mendel, Roos, Napier, Ord Voit[60] and other physiological chemists have noted that thyroid extract increased the excretion of *end*-products of metabolism. Diuresis is likewise increased.

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* *Author's conclusion.*

[52] Kocher: Corresp. f. sch. Aerzte, Bd. xxx, S. 107, 1900.

[53] Elting: Albany Med. Annals, vol. xxv, p. 105, 1904.

[54] Rosa Engelmann: Med. Record, Sept. 22, 1906.

[55] Möllers: Deut. med. Woch., Bd. xxvii, S. 814, 1901.

[56] Leyden: *Ibid.*, Bd. xxvii, S. 477, 1901.

[57] Hutchinson: Brit. Med. Jour., July 16, 1898.

[58] Magnus Levy: *Loc. cit.*

[59] Scholz: Centralbl. f. inn. Med., Bd. xvi, S. 1041, 1069, 1895.

The *diet* is an important feature of the treatment. Meats should be withdrawn as a prophylactic measure after injuries involving the possibility of tetanus, and a milk diet should be insisted upon in developed cases.* Experimental physiology suggests also that total *abstention from animal food,* feeding the patient solely on cereals and other vegetable foods, is even better than the milk diet.*

Briesacher[61] observed that dogs fed on milk bore thyroidectomy better than those given meat, and that their convulsions were fewer. Munk, Allara,[62] Ewald and others found that thyroidectomy was not followed by morbid results in herbivora. So great is the morbid influence of animal food in this connection that it almost imposes itself as the sole cause of the convulsions.

The viscidity of the blood being increased, especially during the convulsions, *saline solution* is indicated as it is in other febrile processes.* It may be used as a beverage or injected intravenously, subcutaneously or rectally, and in large quantities. By promoting osmosis and diuresis, it facilitates greatly the elimination of the blood-poisons. *Blood-letting* or brisk *saline purgation* has been found of value as a preliminary to the use of saline solution.

We have seen that the febrile process tends to reduce the osmotic property of the blood, *i.e.*, to increase its viscidity. Chittenden[63] states that "if the blood is taken for examination during a convulsive seizure," referring to the tetanus of experimental thyroidectomy, "it is *thicker*, contains more solid matter as well as iron and hæmoglobin." Since, as I have shown, adrenoxidase is the albuminous portion of the hæmoglobin molecule, the increase of the latter is accounted for; but the fact remains that its viscidity is increased. Hence, the marked benefit obtained through injections of saline solution by many clinicians. A most convincing test of the value of saline solution is given by the experiments reported by Mathews.[64] "Rabbits were injected with fatal doses of tetanus toxin, and 48 to 60 hours after the injection, when the symptoms of the disease were just appearing, saline infusion was given. In nearly all cases, if taken early, the animals survived, while the control animals died. In well-advanced cases the saline infusion was found to be useless." As observed clinically by McOscar,[95] "free diuresis followed the use of saline," which means a free elimination of toxics, since, as shown by Laulanié,[96] Gley[97] and others, the blood of tetanic animals is more toxic than that of normal ones. Free preliminary blood-letting has been found beneficial by many, owing doubtless to the elimination of toxic wastes and the greater dilution of those remaining in the blood when the saline solution is introduced.

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* *Author's conclusion.*

[60] Cited by Chittenden: Trans. Congr. Amer. Phys. and Surgs., vol. iv, p. 87, 1897.

[61] Briesacher: Archiv f. Physiol., S. 509, 1890.

[62] Allara: Lo Sperimentale, vol. iv, p. 261, 1885.

[63] Chittenden: Trans. Congr. Amer. Phys. and Surgs., vol. iv, p. 93, 1897.

[64] Mathews: Yale Med. Jour., June, 1903.

The *carbolic acid* method recommended by Baccelli has given better results in developed tetanus than antitetanic serum. It is a mistake to believe, however, that "heroic" doses of carbolic acid can be administered with impunity. Such doses tend to depress the adrenal center precisely as does the tetanus toxin, probably because some of it becomes converted into oxalic acid by the adrenoxidase in the blood. Sudden progressive weakness and convulsions, which are also spinal in man, suggest an unfavorable change in the disease, whereas, in truth, the case has been transformed into one of carbolic acid poisoning.* The best results have been obtained by using a 2 to 3 per cent. solution, divided in small doses injected hypodermically every two or three hours, so as to give from 3 to 7 grains (0.2 to 0.5 gm.) in the twenty-four hours. Such doses stimulate the adrenal center actively.*

Italian physicians have obtained better results than those of other countries. In 75 cases collected by D. Symmers[98] from the literature of various countries, including 33 cases treated by Ascoli,[99] the mortality was but 22.66 per cent. The 21 acute cases of the whole series, *i.e.*, those in which the incubation was within ten days, and which usually prove the most fatal, gave a mortality of only 9.5 per cent. It requires large doses to paralyze the adrenal center, but not in all cases. In a child Ebhardt[100] observed intense, though non-fatal symptoms of poisoning, though but 3 grains (0.18 gm.) were being given in the twenty-four hours. Sometimes carbolic acid proved curative where antitetanic serum had failed, as shown by the cases of Laplace,[101] Wagoner[102] and others. Deplano,[103] Mastri[104] and Fabrique[105] recorded seven successful cases in which carbolic acid alone was used.

Other agents have been used more or less successfully, in lieu of those reviewed above. Those that have given satisfactory results in the few cases in which they were tried have been the *iodides*, but only in veterinary medicine, which stimulate the adrenal center;* and *creosote*, 20 minims (1.3 gm.) dissolved in 1 drachm (4 gm.) of olive-oil given subcutaneously, twice daily, which fulfills the rôle of carbolic acid. Various preparations of *mercury*, including calomel, have also been found effective, especially when the patient was rapidly mercurialized and kept so under small doses; this metal is next to iodine in stimulating the adrenal center.*

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* *Author's conclusion.*

[95] McOscar: Amer. Med., Sept. 14, 1901.

[96] Laulanié: C. r. de la Soc. de biol., 9 série, vol. iii, p. 387, 1891.

[97] Gley: *Ibid.*, 10 série, vol. i, p. 192, 1894.

[98] Symmers: Amer. Med., Aug. 15, 1902.

[99] Ascoli: Bull. de la Reale Accad. Med. di Roma, Anno xxiv, p. 496, 1898.

[100] Ebhardt: Gaz. degli Osped., vol. xxiv, p. 1196, 1903.

[101] Laplace: Med. Bull., Mar., 1900.

[102] Wagoner: Phila. Med. Jour., Nov. 4, 1899.

[103] Deplano: Gaz. degli Osped., vol. xxiv, p. 878, 1903.

[104] Mastri: *Ibid.*, vol. xxv, p. 1653, 1904.

[105] Fabrique: Wichita Med. Jour., p. 346, 1904.

Creosote, used in the manner indicated, turned the tide in a case which was steadily sinking under the serum followed by carbolic acid injections, treated by Higginson.[106] "Mercury," administered to the extent mentioned and in conjunction with chloral, is credited with the recovery of three cases treated by Lentaigne.[107] Stoker[108] obtained a similar result. These cases are too few to warrant a conclusion, but, in the light of my views, they indicate that the measures merit further trial.

DRUGS WHICH CONTROL SPASM BY DEPRESSING THE VASCULAR CENTERS.—The convulsions, though the expression in in part of a protective process, are dangerous, because the augmentation of auto-antitoxin—which differs in no way from that produced in other fevers—coincides with excessive irritability of nerve-centers, which characterizes the disease.* The aim, therefore, should be to reduce this irritability, but without diminishing the efficacy of the remedies which directly or indirectly destroy the pathogenic toxin and toxic wastes.* As these provoke their harmful effects by irritating mainly the vasomotor and sympathetic centers, drugs which tend to depress or anæsthetize, as it were, these centers, are indicated.* We have in *chloral hydrate*, the *bromides* and *veratrum viride* precisely such drugs. Used indiscriminately, however, they may do more harm than good. Thus, many convulsions may coincide with a low temperature; the febrile process being inadequate, the blood-poisons steadily increase and the central irritability likewise—the cause of the repeated spasms.* The adrenal center's spurts of activity are obviously for the time being, at least, inadequate to stem the tide. Chloral, or either of the above-named agents, by depressing the activity of the vascular centers, will cause relaxation of all the arteries of the body and produce, therefore, an accumulation of blood in the greater vessels, at the expense of the capillaries.* As it is in the hepatic and cutaneous capillary systems that the antitoxic process is mainly carried on, chloral thus facilitates the accumulation of toxins and toxic wastes and compromises the issue.*

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* *Author's conclusion.*

[106] Higginson: Nashville Jour. of Med. and Surg., May, 1902.

[107] Lentaigne: Brit. Med. Jour., Jan. 8, 1898.

[108] Stoker: *Ibid.*

It is evident, therefore, that vasodilator remedies, *i.e.*, chloral, the bromides or veratrum viride, should not be given when the temperature is low, and that the aim should be to hasten the destruction of toxins and toxic wastes by rapidly increasing the dose of serum, thyroid extract or other remedies to that effect.* To antagonize the spasms, *amyl nitrite* may be used, the inhalation of a few drops just as the spasm is coming on rarely failing to arrest it; its action being ephemeral, it does not antagonize the antitoxic process to any extent.*

The physiological effects of the bromides and chloral clearly point to the recession of blood from the periphery, and the consequent cutaneous hypothermia. "On mammals," says H. C. Wood, "the bromide acts very much as on frogs, inducing progressive paralysis, depression of temperature, and death by asphyxia when given in small poisonous doses." Of chloral, he says: "A most remarkable action of chloral is on the temperature; in this point all observers are in accord with Richardson, of London, who has seen the temperature fall 6° F. in a rabbit. . . . . Hammerstein has found that the fall of temperature is very rapid, 6° C. in an hour, and that it occurs in animals well wrapped up and laid in a warm place." Fortescue-Brickdale,[180] referring to Oré's treatment of tetanus by very large doses of chloral given hypodermically, states that "in all about 30 to 40 cases are on record, but the dangers of the method were eventually found far to outweigh its usefulness." Why should such doses not master the disease if all that is necessary is to prevent spasm? The mode of death in cases thus treated answers the question. "Abbé's patient," for instance, "became *cyanosed* after one injection of 10 gm. (150 grains), and after consciousness was restored died in tetanic spasms." During this peaceful sleep toxins and toxics had accumulated to such a degree that he only awoke to die.

Chloral may be used to advantage, on the other hand, when the temperature is high, to offset the *excess* of vasoconstriction which crowds the blood to the periphery and into the spinal cells as well.* The dose should be regulated, therefore, not with the view to materially reduce the temperature, which indicates the presence in the capillaries of an abundance of auto-antitoxin, but to overcome the enormous and artificial vascular tension which exposes the patient's life, especially during the seizures.* Important in this connection, however, is the fact that the vascular centers, owing to extreme irritability, do not yield to the influence of ordinary doses; 20 grains (1.3 gm.) every four hours are usually required to produce any effect in an adult. If such or larger doses do not lower the temperature materially, although they reduce the number of seizures, they may be regarded as beneficial without interfering with the curative process.*

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* *Author's conclusion.*

[180] Fortescue-Brickdale: Lancet, May 20, 1905.

The resistance of the vascular centers, when hyperirritable, to the benumbing effects of chloral is illustrated by Maberly's[110] successful case, in which 20 grains (1.3 gm.) every three hours proved futile. On increasing the dose to 60 grains (4 gm.), however, the spasms were controlled *without* reducing the temperature, thus showing that the enormous vascular tension alone had been mastered. That chloral can reduce the temperature in tetanus may be illustrated by Llewellyn's[111] case, in a boy aged 11 years, in which 20 grains (1.3 gm.) every four hours brought the temperature from 103° F. (39.5° C.) to below 101° F. (38.3° C.), "the pulse occasionally dropping to nearly 80."

The same principles govern the use of the *bromides*, but as these salts, when given in large doses, also depress the adrenal center,* they should be used only when chloral loses its effect. The best results are obtained by combining the potassium, ammonium and sodium salts, the latter forming one-half of the dose. *Veratrum viride* is endowed with properties similar to those of chloral hydrate and does not depress the adrenal center. Large doses are also required. In prescribing this remedy, the fact that the tincture as now prepared (1905 U. S. P.) is four times weaker than formerly should not be overlooked. *Curare* has been recommended by some observers and condemned by others—owing, doubtless, to the very unreliable preparations available in the average shop. This applies likewise to *physostigma, i.e.*, calabar bean.

In the case of a boy of 11 years, Grinnell[112] found hourly doses of the older tincture ineffectual with similar doses of the fluid extract of gelsemium. It was only when three drops of each, *i.e.*, 12 drops of the new U. S. P. tincture of veratrum, were given hourly that the spasms were controlled, the case ending favorably.

Drugs Which Control Spasm by Causing Constriction of the Peripheral Arterioles.—The drugs are useful in that they increase the effects of those just reviewed. When, for instance, chloral has depressed the vasomotor centers sufficiently to cause recession of the peripheral blood, *morphine* given hypodermically in ordinary doses will stimulate the sympathetic center sufficiently to arrest the propulsive activity of the arterioles, and, by thus reducing the caliber, limit still further the quantity of blood admitted into the capillaries. When, therefore, chloral is beginning to lose its effect an occasional injection of morphine may be used advantageously to sustain it. *Antipyrin* and *acetanilid* act in the same way.

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* *Author's conclusion.*
[110] Maberly: *Ibid.*, May 6, 1905.
[111] Llewellyn: Brit. Med. Jour., Feb. 15, 1896.
[112] Grinnell: Med. News, July 18, 1896.

It would appear as if the central erethism would render small doses of morphine adequate to *stimulate* the sympathetic center; but such is not the case. Trousseau and Pidoux[118] many years ago held that large doses were alone effective. This is readily accounted for, however, when the marked vascular tension present in tetanus is taken into account. Unless violently stimulated, the arterioles cannot contract upon the tense arterial column. Hence the advice I submit, to give it in ordinary doses, but only *after* the arterial tension has been already reduced.

EPILEPSY.

SYNONYMS.—*Falling Sickness, Falling Evil, Falling Fits, Morbus Sacer, Morbus Caducus.*

Definition.—Epilepsy, a chronic disease characterized by periodical convulsions accompanied usually by unconsciousness, is due to inherited or acquired hypoactivity of the adrenal system and to the resulting accumulation of toxic wastes in the blood. As this entails a marked rise of vascular tension, an excess of blood is driven into all capillaries, including those of the spinal system and cortex. Both the latter being thus rendered hyperexcitable, a fit occurs when this hyperexcitability is suddenly increased by the appearance in the blood of an excess of auto-antitoxin, the result, in turn, of a sudden resumption of defensive activity by the adrenal system when the blood becomes sufficiently toxic to enforce it. The fit lasts until the toxic wastes are converted more or less efficiently into harmless and eliminable end-products.*

Symptoms and Pathology.—Three types are recognized: minor epilepsy, or petit mal; major epilepsy, or haut mal, or grand mal; and Jacksonian epilepsy.

In *minor epilepsy* there may be a brief loss of consciousness, and perhaps slight clonic spasms of the face and limbs, but only entailing, as a rule, a temporary cessation of the conversation or occupation in which the patient may be engaged. He suddenly becomes pale, his face assumes a blank expression, but after a few seconds he recovers and resumes the sentence or act he had begun before the spell. Occasionally the patient falls into coma which is usually attended with stertorous breathing suggesting apoplexy. In minor epilepsy clonic convulsions are never witnessed.

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* *Author's definition.*

[118] Trousseau and Pidoux: "Traité de thérapeutique," Paris, 1875.

An attack of *major epilepsy* is sometimes preceded by ringing in the ears, tingling, general malaise, epigastric uneasiness, etc., but a common prodrome is the *aura*, which occurs in about one-half of the cases. This may consist of sensory phenomena, *i.e.,* pain, sensations of heat or cold, or of a breeze striking an extremity and traveling upward towards the body; or of aural, visual, olfactory or gustatory hallucinations, such as roaring sounds, flashes of light, unpleasant odors, etc. Or again, the aura may manifest itself by motor phenomena, a marked tremor or an irresistible tendency to use the muscles, to gesticulate or to run, the so-called "procursive" epilepsy. Finally, it may be attended by physical phenomena; sudden terrors, mental exuberance or hallucinations as to the presence of strangers, or bearing upon long-past events, etc. The aura may be very short, a few seconds, or endure sufficiently long to enable the patient to protect himself against the oncoming convulsion, by sitting or lying down. In rare instances it lasts thirty minutes or more.

All these phenomena clearly betoken erethism, *i.e.*, undue stimulation of the motor or sensory organs involved. The aura is, in fact, the beginning of the convulsive paroxysm.

Spratling[114] states that "there is a growing tendency for some years past to regard the aura as essentially constituting a part of the epileptic fit," and considers it as such himself, advising, moreover, that such cases be treated accordingly. This conclusion was based on a study of 1325 cases at the Craig Colony. Of these 45 per cent. had auras.

When the fit begins the patient usually utters a loud cry, due to sudden contraction of the muscles of the chest and larynx. Three symptoms occur simultaneously at this time, *i.e.*, the "epileptic cry," unconsciousness and fall—the patient dropping like a log. A *tonic* spasm of all the flexors follows: the legs being extended, the fingers, hand, forearm flexed, the head thrown back and turned to one side; the eyes also turn up or aside. This rigid state of all the muscles lasts usually but a few seconds.

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[114] Spratling: Med. News, July 18, 1903.

The transition from the state of rigidity to that of *clonic* spasm is usually marked by a momentary tremor. When the true fit begins the extremities are thrown about violently, sufficiently so at times to produce dislocations. The head is tossed from side to side, the eyes roll in their orbits, the lids open and close rapidly and the tongue is protruded and withdrawn, provided it is not caught between the teeth by the jaws, whose muscles are likewise contracted with violence—causing disfiguring distortions. The bitten tongue often causes the saliva, itself converted into foam by the churning to which it is submitted, to become streaked with blood, and the patient is said to "froth at the mouth." The urine and fæces are sometimes involuntarily voided, owing to contractions of the intestinal walls. The pallor of the clonic stage has now disappeared and becomes replaced by a dusky, cyanotic hue, the features being swollen, and usually, as is the case with the rest of the body, covered with sweat.

This paroxysm only lasts, as a rule, a couple of minutes. The violence of the contractions becomes gradually less, and the patient lapses into a comatose state attended by stertorous breathing. Finally he falls into a deep sleep. On waking, some lassitude and muscular pain may be complained of, but on the whole, the patient, recollecting nothing of the paroxysm, seems hardly to have suffered from the experience. Occasionally the full return to consciousness is preceded by "postepileptic states," during which the patient may perform automatic acts, undressing, etc., such as those ascribed to somnambulism. He may also become suddenly maniacal and violent, sufficiently so at times to commit murder. Marked weakness, paresis, tremor, aphasia and kindred nervous phenomena may also be witnessed, but these rarely last more than a few hours.

These attacks occur with more or less frequency. From the practically continuous paroxysms, lasting hours and even days, constituting the *status epilepticus*, during which the patient may die of exhaustion, to the rare instances in which years elapse between the fits, there are gradations innumerable. In the majority of cases, however, they occur at intervals of a few days.

A *Jacksonian* paroxysm is often preceded by an aura, which may be motor, such as tremor or rapid contractions of the toe, thumb, etc., first affected, or sensory, tingling, paræsthesia, etc. The special senses may also be the source of phenomena such as those witnessed in the aura of major epilepsy. The tonic phase of the latter form is also present, but to a very limited degree, and may not occur at all.

While the spasm may be restricted to a limited number of muscles corresponding with a given cortical lesion, the irritation of the latter often spreads to contiguous motor areas, so that several groups of muscles may be involved. It may thus creep up the arm to the shoulder and face, and involve the whole side of the body; or up the leg, the body, and face; or, again, begin at the face and proceed downward. Finally, it may become general, when a typical attack of major epilepsy occurs. While this gradual progression occurs, the patient remains conscious and it is only when certain regions, including the face, are involved, that consciousness is lost. After the paroxysm, which lasts but three to five minutes, the region affected may be numb and paralyzed and remain so from a few hours to several days. After a time this may become permanent.

Etiology and Pathogenesis.—The *tonic* spasm is produced in the same manner as the corresponding though more severe spasm of tetanus* (*q.v.*). Instead of terminating as such, however, it soon lapses into the typical epileptic paroxysm, the clonic fit.

The impulses which cause *clonic* convulsions are primarily derived from the cerebral cortex, the spinal system being used as the mechanical intermediary for their production, and are of the nature of voluntary impulses to the spinal system.*

A striking feature of this stage is the similarity of the movements to those carried on voluntarily. Thus, to turn the eyes from one direction to the other, to throw the head backward, to bend and unbend the arm at the elbow, are all, at other times, voluntary movements. The performances during the postepileptic states, which M. Allen Starr termed "psychical equivalents," also point to the source of the impulses that evoke the movements, namely, the cortex. As I have pointed out elsewhere, the latter does this *only* by exciting the appropriate cells in the spinal system, the sole source of motor impulses. Indeed, Prus[116] has shown that excitation of the cortex caused typical convulsions even after division of the pyramidal tracts, the impulses passing by way of the tegmentum and pons—a conclusion confirmed experimentally by Bischoff,[117] Hering[118] and others. Long before, in fact, Magnan[119] had caused epileptic seizures in animals deprived of their hemispheres, while Vulpian[120] had been led to conclude by a series of experiments that the center for epileptic convulsions was located at the *base* of the brain. It is evident, therefore, that the basal structures can provoke clonic as well as tonic spasms.

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* *Author's conclusion.*

The persistence of clonic convulsions after division of the pyramidal tracts simply shows that these represent but a portion of the link-system between the brain and the spinal cord; and that impulses from the cortex can excite the upper extension of the cord in the third ventricle. Where they reach the basal cells is suggested by one of Bischoff's conclusions, namely, that "after destruction of the optic thalamus, the hypothalamic region and the pyramidal path on one side, faradic irritation of the homolateral motor cortex remains without effect." As we have seen, it is in the hypothalamic region that the cortical paths meet those from the pituitary body, which pass downward and finally reach the cord. In the normal animal, including man, of course, the entire spinal gray matter receives spasmogenic impulses from the cerebrum.

The clonic convulsions are the result of a temporary and intense hyperæmia of the cerebral cortex, due in turn to general vasoconstriction.* The cortex being a sensory organ, this marked congestion—during which the speed of the blood-streams is greatly increased—provokes a storm of impulses to the spinal system—itself hyperæmic and oversensitive—which the spinal motor cells convert into motor impulses and transmit to the muscles (which are also hyperæmic and overexcitable), thus inciting the clonic fit.*

The neuroglia being plasma capillaries,* they bear the brunt of the excessive blood-pressure to which the nervous elements are submitted,* and if the disease is not treated early, more or less extensive gliosis occurs and the chances of recovery are correspondingly reduced.

As I have pointed out,[121] the neuroglia fibers and cells are channels for blood-plasma containing adrenoxidase granules. Pierce Clark and Prout[122] recently wrote: "The neuroglia hyperplasia in epilepsy is now almost constantly found. With improved methods and technique it will probably be demonstrated in every case of considerable duration." Chaslin,[123] who first pointed out this condition, ascribed it to a constitutional vice of development, but the identity of neuroglia fibers as capillaries alone accounts logically for it. Many investigators, Féré, Koppen, Hohne, Bratz, Anglade[134] and others, have confirmed Chaslin's observation. Victor Horsley has[135] emphasized the importance of congestion of the cortical mantle in the production of fits. Féré and Chaslin, Pierce Clark and others found diffuse gliosis in cases of long standing. Ito[136] produced typical fits in guinea-pigs by causing traumatic hyperæmia of the cortex.

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* *Author's conclusion.*

[116] Prus: Wiener klin. Woch., Bd. xi, S. 857, 1898.

[117] Bischoff: *Ibid.*, Bd. xii, S. 961, 1899.

[118] Hering: *Ibid.*, Bd. xii, S. 831, 1899.

[119] Magnan: Arch. de physiol. norm. et path., vol. v, p. 115, 1873.

[120] Vulpian: C. r. de l'Acad. des sci., Apr. 27, 1885.

[121] *Cf.* this vol., chapter fifteenth.

[122] Pierce Clark and Prout: Amer. Jour. of Insanity, vol. lx, p. 645, 1904.

[123] Chaslin: Arch. de méd. exper. et d'anat. path., vol. iii, p. 305, 1891.

The participation of the vasomotor system, as shown by the general vasoconstriction, is as clear. Spitzka, in 1881, attributed the fit to the "explosive activity of an unduly irritable vasomotor center," and epilepsy is now commonly referred to as a "functional vasomotor disease." A continuous rise of pressure during the fit was noted by François-Franck and Pitres. The speed of the blood-stream is greatly increased at this time—three to five times in the muscular vessels, according to Hill[137]—an index of the violence of the cortical circulation. Even the skin shows evidence of this sometimes by minute capillary hæmorrhages, as observed by Aldrich[138] and others. Weber,[139] moreover, found vascular lesions and extravasations in the cortex and medulla of cases of status epilepticus, so great had been the capillary pressure—the identical pressure which projects the blood-plasma into the neuroglia fibers.*

Chaslin always found the hyperplasia most advanced in the *superficial* layer of the cortex, though it involved the subjacent strata. Blocq and Marinesco[140] found as the most constant lesion in the psycho-motor zone of nine cases, vascular alterations and hyperplasia of the neuroglia, associated with punctiform hæmorrhages in other parts of the nervous system in every instance. The cortex being regarded as a sensory organ, its uppermost layer thus becomes the most active in the production of the convulsions. Indeed, Prus[141] found that even electrical excitation of the cortex could not provoke fits after the application of a cocaine solution had anæsthetized its surface, thus identifying the cerebral gray matter as the source of the spasmogenic impulses.

The excessive vasoconstriction and rise of blood-pressure which gives rise to this cortical hyperæmia, is due to irritation of the vasomotor and sympathetic centers by toxic waste-products.* Epileptic convulsions differ from convulsions produced by many exogenous poisons (strychnine, for instance) in that they are due to poisons or toxins formed in the body.*

"Certain drugs, notably absinthe," writes Schäfer,[142] "produce, when injected into the vascular system, convulsive attacks which are scarcely distinguishable from the epileptic fits provoked by stimulation of the cortex cerebri." That all such drugs provoke a marked rise of the blood-pressure may be shown by comparison with a few of the many other spasmogenic agents. Thus, while absinthe was found to cause intense congestion of all organs examined by Pauly and Bonne,[143] Wood[144] states that "the full dose of strychnine produces a rise of the arterial pressure which is enormously increased during the convulsion." He also refers[136] to the observation of Bezold and Bloebaum, "that when a small dose of atropine is injected into the carotid artery—that is, near the vasomotor centers—," he adds, "there is an instantaneous rise of blood-pressure"—"a great rise," as he afterwards says. Cocaine, as shown by Von Anrep, causes "convulsive movements of cerebral origin," which "are arrested by section of the spinal cord;" Wood also says: "Certainly the evidence is overwhelming that cocaine directly increases the blood-pressure." The fits are precisely those of epilepsy; the syndrome is known as "cocaine epilepsy." Alcohol can likewise produce both minor and major epilepsy. Wood and Hoyt[137] concluded, after a recent experimental study, that the excitement it caused was due to the "enormously increased flow of blood running riot through the cerebrum."

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* *Author's conclusion.*

[134] Anglade: Arch. de neurol., 2 série, vol. xiii, p. 418, 1902.

[135] Victor Horsley: Brit. Med. Jour., Apr. 2, 1892.

[136] Ito: Deut. Zeit. f. Chir., Bd. lii, S. 417, 1899.

[137] Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 155, 1900.

[138] Aldrich: Med. News, May 26, 1900.

[139] Weber: Wiener med. Woch., Bd. xlix, S. 158, 1899.

[140] Blocq and Marinesco: Semaine méd., vol. xii, p. 445, 1892.

[141] Prus: *Loc. cit.*

[142] Schäfer: "T. B. of Physiol.," vol. ii, p. 721, 1900.

[143] Pauly and Bonne: Gaz. hebd. de méd. et de chir., May 13, 1897.

[144] Wood: *Loc. cit.*, thirteenth edition, p. 217, 1906.

L. Pierce Clark,[138] after a study of 150,000 seizures, we have seen, concluded that "we must see the principle of pathogenesis in an initial toxin or autointoxication," *i.e.*, "an accumulation of waste-products." Van Gieson[139] and other authorities have also noted greater frequency of fits during gastro-intestinal disturbances and constipation, the blood at the time being especially toxic. This view, which has a large number of supporters, is sustained by the beneficial effect of appropriate dietetic measures. The relation between epilepsy and other disorders attributed to toxic wastes points in the same direction. Spiller,[140] Bernhardt[141] and others have laid stress on its relationship with migraine, Trowbridge[142] with chorea, etc.

When the antitoxic powers of the blood are taken into account, however, it becomes evident that only very toxic fluids derived from epileptics will prove pathogenic in experimental animals. Herter,[143] for instance, obtained results in rabbits differing but little, if at all, from those produced by normal blood, with defibrinated blood taken from epileptics, but when he used blood-serum of exceptional toxicity obtained from an epileptic with prolonged headaches, habitually an overfeeder at meals and with *congested face and conjunctivæ*, 10 c.c. ($2^1/_2$ drachms) sufficed to kill rabbits in 45 minutes, after the animals had had tonic and clonic spasms and become somewhat cyanotic. Kraïnsky[144] produced characteristic seizures in rabbits in two and three minutes, and several recurrences, with blood-serum obtained by cupping from a case in status epilepticus. Savary Pearce and Boston[145] found that several injections of blood from an epileptic into rabbits caused an enormous leucocytosis, reaching in one instance 162,800 per cm.—a proof that the adrenal system was violently stimulated.

The toxic substances which incite the convulsions are formed when the breaking down of worn-out tissue-cells, tissue-proteid, focal toxins, etc., is not carried to a finish, *i.e.*, when this process is not sufficiently active to lead up to the formation of benign, eliminable substances—urea and uric acid, etc., the normal end-products.* **But it is only when this accumulation**

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* *Author's conclusion.*

[136] Wood: *Loc. cit.*, thirteenth edition, p. 171, 1906.

[137] Wood and Hoyt: Memoirs National Acad. of Sci., vol. v, 1905.

[138] L. Pierce Clark: Med. News, July 18, 1903.

[139] Cited by House: Buffalo Med. Jour., June, 1896.

[140] Spiller: Amer. Jour. Med. Sci., Jan., 1900.

[141] Bernhardt: Deut. Aerzte Zeit., July 15, 1900.

[142] Trowbridge: Alienist and Neurologist, Jan., 1892.

[143] Herter: Jour. of Nerv. and Mental Dis., Feb., 1898.

[144] Krainsky: Wiener klin. Woch., Bd. xi, S. 185, 1898.

[145] Savary Pearce and Boston: Medicine, Feb., 1904.

has reached a certain degree that epileptic seizures occur; thus, it may only be sufficient to give rise to the tonic spasm, *i.e.*, minor epilepsy; or it may exceed this limit and produce clonic convulsions, major epilepsy.*

Such being the case, it is evident that the cause of the disease is deficient activity of the process through which the worn-out living tissues are broken down. This process being carried out by trypsin, whose activity is governed by the heat-energy it receives through the interaction of nuclein and adrenoxidase, it follows that insufficiency of either of these bodies underlies the morbid process. It cannot be the nuclein, since this is derived from the food. The production of the tissue-ferment—or rather of the proferment—by the pancreas being proportionate with the secreting activity of this organ, and this function in turn being governed by the proportion of adrenoxidase in the blood, we are brought to *inadequate activity of the adrenal system as the primary cause of epilepsy.**

This insufficiency of the adrenal center is thus pathogenic in two ways: it entails (1) imperfect catabolism and the resulting accumulation of toxic wastes in the blood; (2) inadequate conversion of these poisons in the blood and liver into eliminable products, *i.e.*, imperfect protection of the organism.*

This does not mean, however, that the test-organ does not respond to the stimulating influence of the circulating poisons: it only fails to do so adequately.* Accustomed to the presence of tissue-wastes, and even to that of these particular poisons in the blood circulating through it, it responds only when these have accumulated in great quantities, and then, by a spurt of activity which soon recedes, relieves the blood of at least some of its spasmogenic toxics by increasing markedly the production of auto-antitoxin.* These exacerbations of activity coincide with the convulsions.*

Briefly, the accumulation of toxic wastes in the blood violently stimulates the *three general centers of the blood-vascular system*, the sympathetic, vasomotor and adrenal centers, *simultaneously*, and although the rôle of the adrenal center is a protective one, it is to this collective action that the convulsions are due.*

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* *Author's conclusion.*

Waste-products, we have seen, are thought by many observers to provoke epileptic seizures. The identity of the specific agent is not established, however. Haig incriminated uric acid, but his view has not been sustained. As previously stated, uric acid is a benign end-product. Kraïnsky[146] attributed the fits to a diminution of the uric acid formed, the true spasmogenic substance being an intermediate product essential to the formation of uric acid, *i.e.*, ammonium carbonate. It proved not only highly toxic, but it produced, when injected in animals, typical epileptic seizures. Inouye and Saiki[147] attribute them to a dextro-rotatory lactic acid found increased in the blood after severe attacks, and which unites with urea to form dialuric acid, then uric acid. Both these views are sustained by an exhaustive study of Herter and Smith,[148] in which they found an excess of uric acid in the urine only *after* the convulsions. Teeter[149] also found that it contained a larger amount of urea than during the intervals, when it was very low. Rachford, in 1895, ascribed migraine, "migrainous" epilepsy and other periodical affections to paraxanthin poisoning. The poisonous ptomaine cholin, found by Mott and Halliburton in blood and cerebro-spinal fluid in cases of nervous disease, has also been considered as the spasmogenic agent by Donath,[150] Coriat[151] and others. When we consider that nervous, hepatic, muscular and other heterogeneous tissues are all the seat of imperfect catabolism and other facts, however, it is probable that the convulsions are caused by several poisons acting more or less collectively.* Thus, Ohlmacher[152] found a persistent thymus in several cases; Murdoch[153] and others have cured cases that were clearly due to gastro-intestinal disorders, etc.

The connection with the anterior pituitary body, as adrenal center, is suggested in various ways. We have seen that removal of the pituitary or of the adrenals provokes convulsions. Langlois[154] long ago showed that the adrenals, in some unexplained way, "annihilated the toxic substances produced in the course of chemical exchanges." He concluded that "there was every reason to suppose, however, that it was through an oxidation process." With adrenal secretion as the basis of oxidase, we have a clear index in the fact that while there are frequently abnormally low temperatures during health, as observed by Lemoine and others, a rise occurs during seizures which sometimes is very great. Charcot, Bourneville and others have laid stress on this feature. Clark and Prout[155] found that in status epilepticus, the height of the curve corresponded with the severity of the attack, sometimes reaching 107° or 108° F. (41.6° or 42.2° C.). This applies to ordinary cases as well; thus Benedikt[156] reported a case in which it sometimes rose to 109.4° F. (42.8° C.). If this is connected with an antitoxic process, an intercurrent disease, by raising the functional activity of the test-organ (which fails to respond promptly *only* to the physiological poisons to which it has become habituated), should prove beneficial. Hippocrates, Van Swieten, Esquirol and other masters have laid stress on the favorable influence of various diseases on epilepsy. Recent writers, Féré, Voisin, Lannois, Lenoir[157] and others have done likewise. Hessler[158] and Lannois[159] have even used bacterial injections on this plea. Pierce Clark and Sharp[160] have found, however, that a temporary improvement is all that is obtained by an intercurrent disease—which means, interpreted from my standpoint, that the adrenal system, whipped up for a while, soon lapses again into its lazy habits.

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* *Author's conclusion.*

[146] Kraïnsky: *Loc. cit.*

[147] Inouye and Saiki: Hoppe-Seyler's Zeit. f. physiol. Chemie, Bd. xxxvii, S. 203, 1903.

[148] Herter and Smith: N. Y. Med. Jour., Sept. 3, 1892.

[149] Teeter: Amer. Jour. of Insanity, Jan., 1895.

[150] Donath: Hoppe-Seyler's Zeit. f. physiol. Chemie, Bd. xxxix, S. 526, 1903.

[151] Coriat: Amer. Jour. of Physiol., Dec. 1, 1904.

[152] Ohlmacher: Amer. Jour. of Insanity, Apr., 1898.

[153] Murdoch: Med. News, July 15, 1905.

[154] Langlois: Richet's "Dict. de Physiol.," vol. i, p. 145, 1895.

[155] Clark and Prout: Med. Record, Nov. 24, 1900.

[156] Benedikt: Intern. klin. Rundschau, Nu. 46, 1891.

[157] Lenoir: Thèse de Paris, 1901.

[158] Hessler: Jour. Amer. Med. Assoc., May 14, 1898.

The main predisposing causes of idiopathic epilepsy are such as tend to inhibit the functional efficiency of the anterior pituitary body's test-organ.* The preponderance of this disease during youth is due mainly to one of two causes: (1) numerous diseases during childhood, which tend to debilitate this organ by stimulating excessively the pituitary body and through it the adrenals during development; (2) inherited general debility through the presence in parents of diseases or habits, such as tuberculosis, syphilis, alcoholism, etc., which tend to impair to a marked extent the test-organ's sensibility.* Epilepsy may also follow typhoid fever, influenza and other diseases, owing to this morbid influence on this organ.

Over twenty years ago I[161] emphasized, after studying 40 cases, the predisposing importance of numerous children's diseases to hay-fever, a disease due also to the accumulation of toxic wastes in the blood. Out of 19 of these cases in which no heredity could be traced, 82 per cent. had had four children's diseases, while many of these, *i.e.*, 55 per cent. of the total, had had six. Bessière,[162] in a series of carefully analyzed cases of major epilepsy, could only ascribe one-sixth to hereditary influence, while in the other 152 cases infectious diseases and convulsions showed "an enormous preponderance in the antecedents." . . . . "The infectious process," says this observer, "leaves on the organism a profound impression, the nature of which is still to be determined." Out of 2000 cases studied by M. Allen Starr,[163] 68 per cent. had epilepsy before twenty years of age, *i.e.*, "during brain development." The neural portion of the pituitary body being an embryological offshoot of the brain-segment, it follows that it must participate in the morbid process. Indeed, the relationship between this organ and the osseous system is well shown by the overgrowth of bones attending its overactivity in acromegaly; that the opposite condition exists in epilepsy is evident. Gowers[164] found a history of rickets in nearly 75 per cent. of 100 cases studied.

The transmission of epilepsy has been affirmed by Obersteiner[165] and others, but, from my viewpoint, the patient inherits only a depraved condition of the test-organ. Hence the fact that experimental epilepsy in guinea-pigs, as noted by several investigators, has failed to sustain Obersteiner's view. The predisposing influence of debilitating diseases, tuberculosis, syphilis, alcoholism, etc., in parents is generally acknowledged, and is readily accounted for by the morbid action of such diseases (*q.v.*) on the pituitary body. Examples in which various diseases started epilepsy are numerous. Bourneville and Dardel[166] observed a case in which typhoid fever caused both epilepsy and idiocy in a previously normal subject. In one of Gélineau's[167] it followed influenza. In one reported by Clark and Sharp[168] measles converted an ordinary epilepsy into status epilepticus, etc.

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* *Author's conclusion.*

[159] Lannois: Lyon médical, vol. xcv, p. 37, 1900.

[160] Pierce Clark and Sharp: Med. News, Dec. 1, 1900.

[161] Sajous: "Lectures on Dis. of the Nose and Throat," p. 176, 1885.

[162] Bessière: Thèse de Paris, 1895.

[163] M. Allen Starr: Med. News, Jan. 9, 1904.

[164] Cited by Ohlmacher: Amer. Jour. of Insanity, Apr., 1900.

[165] Obersteiner: Neurol. Centralbl., Bd. xix, S. 498, 1900.

Emotional shock and fright, by imposing too suddenly a severe stress upon the cellular elements of the posterior pituitary (as *sensorium commune*), may also provoke typical epilepsy, by impairing permanently their sensitiveness.* A constant flow of impulses from the periphery may initiate the form known as "reflex" epilepsy by fatiguing the organ's nerve-cells and similarly depressing its sensibility to impressions received through the anterior lobe and awakened by blood containing physiological waste-products.* The convulsions are caused by these wastes precisely as in typical cases of epilepsy, both in the reflex form and in that due to emotions, the former ceasing when the peripheral exciting cause is removed.*

Spratling[169] states that emotional shock and fright as causes of epilepsy do not receive the attention they should. In 1323 cases he traced 62 to this cause, some supervening immediately. Females around puberty predominate. In the 2000 cases studied by M. Allen Starr,[170] 119 were due to fright. The intense pallor, the relaxation of sphincters, the fainting, etc., often witnessed under such conditions exemplify the intensity of the shock upon the true *sensorium commune, i.e.*, the neural lobe of the pituitary, especially its sympathetic center.

As to reflex epilepsy, Brubaker[171] collected 15 cases in which irritation of the dental nerve, diseased or misplaced teeth caused epilepsy. Cases cured by the removal of aural growths or carious ossicles, etc., have been numerous. Ranney,[172] Gould[173] and others have reported cases cured by correcting defects of accommodation. Kafemann[174] found adenoids frequently in epileptics. Recently, St. Clair Thomson[175] reported a case six years after cessation of the seizures, cured by the removal of adenoids. Intestinal worms, phimosis, vesical and renal calculi, scars, etc., and many other morbid conditions may thus provoke epilepsy by control irritation transmitted by afferent sensory nerves, the fifth pair in the case of the head. A typical form of reflex epilepsy is that due to nasal exostoses, hypertrophies, etc. We have seen that Prus, by anæsthetizing the cortex with cocaine, prevented the fits caused by local excitation. Ten Siethoff[176] arrested oncoming fits in a man who had had epilepsy 20 years, by applying a 10-per-cent. solution of cocaine to the nasal mucous membrane; removal of neoplastic tissue therein cured the case. Similar instances have been reported by others. Now, Cyon, we have seen, observed that immediately after removal of the pituitary body any amount of irritation, even ammonia, failed to excite reflex reactions which before the operation were readily obtained.

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* *Author's conclusion.*

[166] Bourneville and Dardel: Progrès médical, vol. xxvi, p. 28, 1898.

[167] Gélineau: Indépend. médicale, Mar. 21, 1900.

[168] Clark and Sharp: *Loc. cit.*

[169] Spratling: Amer. Medicine, Sept. 16, 1905.

[170] M. Allen Starr: *Loc. cit.*

[171] Brubaker: Jour. of Nerv. and Mental Dis., Feb., 1898.

[172] Ranney: N. Y. Med. Jour., Feb. 3, 10, 17, 1894.

[173] Gould: Amer. Medicine, July 5, 1902.

[174] Kafemann: Sarasohn: Dissert. Königsberg; Inter. Centralbl. f. Laryn., Rhin., u. verwandte Wissen., Nov., 1895.

[175] St. Clair Thomson: Practitioner, May, 1905.

[176] Ten Siethoff: Ann. des mal. de l'oreille, du larynx, etc., July, 1895.

Jacksonian epilepsy differs from major epilepsy in that the cortex is the seat of a circumscribed lesion which, when hyperæmia of the brain of the kind just described occurs, serves as a local excitant. The cerebral lesion being localized, the impulses transmitted to the cord cause it to provoke clonic convulsions only in the group of muscles over which the area involved presides. So true is this that if the starting point of the premonitory tingling or numbness be carefully noted, *i.e.*, a toe, the fingers, the face, etc., Seguin's "signal symptoms," the location of the cerebral lesion may be exactly determined (cerebral localization), and the offending structure—a glioma, sclerotic patches, tumors, a syphilitic gumma, depressed bone, etc., in the motor zone in the great majority of instances.

In such cases the lesion acts as a foreign body, against which, when undue hyperæmia of the brain occurs, the cortex is projected and subjected to localized pressure and irritation—the spasmogenic factor.*

The evidences of secondary hyperæmia are also present in such cases at the site of the cortical lesion. Thus Joseph Collins[377] found in excised cortical tissue not only distention of the vessels with thickening and infiltration of their walls, but also proliferation of neuroglia. That marked vascular tension prevails is shown by occasional occurrence of cerebral hæmorrhage in young subjects, as in a case reported by Struppler;[378] the presence of congestion is shown by the choked disk, as in cases reported by Burr and W. J. Taylor,[379] evidence that we have here also the required pressure to engorge the neuroglia. From this to the formation of sclerosis there is but a step. Thus, Anglade[380] never found the neuroglia normal, and in some regions it had proliferated in the form of plaques, *i.e.*, areas of sclerosis.

Treatment.—The prevailing medicinal treatment of epilepsy may be said to resolve itself into the use of depresso-motors to prevent the convulsions. In the light of the foregoing evidence these agents, while reducing the number of seizures, simultaneously aggravate the morbid process.*

Measures Which Tend to Enhance the Accumulation of Waste-products in the Blood.—*Bromide Salts.*—The primary action of these salts is to depress the functional activity of the general vasomotor center, producing thereby relaxation of all the arteries.[*] By thus causing the blood to accumulate in the great central trunks, the proportion of blood circulating in the capillaries of all organs and the periphery is correspondingly reduced and the activity of intracellular metabolism is lowered in proportion.[*] This morbid process is aggravated by the fact that the bromides simultaneously reduce the sensibility of the adrenal center.[*] By thus diminishing the quantity of adrenal secretion supplied to the blood, they impair its catabolizing properties, and inhibit, therefore, the conversion of toxic wastes into eliminable products.[*] These pathogenic influences are proportionate, all else being equal, with the quantity administered in a given time.

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* *Author's conclusion.*

[377] Joseph Collins: Brain, vol. xix, p. 388, 1896.

[378] Struppler: Deut. med. Woch., Bd. xxvi, S. 191, 1900.

[379] Burr and Taylor: Amer. Jour. Med. Sci., July, 1902.

[380] Anglade: *Loc. cit.*

The action of the bromides on the vasomotor center has been shown in the department of Pharmacodynamics. The paralyzing action on the adrenals is sufficient in some instances to cause bronzing similar to that of Addison's disease. Bourneville and Chapotin[181] refer to Echeverria,[182] "who saw a case in which the brow and neck were markedly pigmented brown," and to cases witnessed by Voisin; in one of these "the skin of the face was a dark, dirty yellow," in the other it was "covered with bronze patches having no connection with the acne." The harmful effects of the bromides are being generally recognized. F. Peterson[183] has reported 11 cases in which withdrawal or marked reduction of the drug was followed by great diminution of the number of seizures. "In some of these cases," says this neurologist, "the improvement is startling." Spratling,[184] after close study of the results in several thousand cases at the Craig Colony, concludes that "we must not only regard the bromides as powerless to cure epilepsy," but also "as capable of doing as much harm as they do good, as they are ordinarily administered." Moreover, as Percy Bryant[185] rightly states, the bromides have added another disease in many epileptics, *i.e.*, bromism.

The bromides have been administered with *adonis vernalis*, as Bechterew's method, and with *digitalis*, as recommended by Huchard; but the recession of the blood from the tissues, caused by the bromides, thwarts the effects of these agents, and the cases on record do not seem to have afforded results other than those afforded by the salts themselves in corresponding doses.

OTHER DRUGS WHICH TEND TO INHIBIT TISSUE METABOLISM.—Many such have been and are being used. Their main action is alone given in this connection, the reader being referred to the department of Pharmacodynamics for additional details and evidence. *Chloral, chloralose* and *paraldehyde* are even more pernicious than the bromides, since they depress primarily the adrenal center and therefore the activity of tissue metabolism and oxidation in the blood-stream. *Sulphonal* and

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[*] *Author's conclusion.*

[181] Bourneville and Chapotin: Progrès méd., vol. xxix, p. 1, 1900.

[182] Echeverria: Phila. Med. Times, Nov. 23, 30; Dec. 7, 14, 1872.

[183] F. Peterson: N. Y. Med. Jour., Sept. 25, 1897; Amer. Medicine, June 24, 1905.

[184] Spratling: N. Y. Med. Jour., Aug. 19, 1905.

[185] Percy Bryant: State Hosp. Bull., Oct., 1896.

trional produce similar effects in a different way: being active reducing agents, they diminish the oxygenizing and oxidizing (antitoxic) power of the blood, by robbing it of its oxygen. They inhibit the seizures by reducing the vital activity of all organs, including the nerve-centers.

Opium, used in increasing doses, as in Flechsig's method, sometimes diminishes the number of seizures. It does this by causing constriction of the arterioles, thus reducing the speed of the blood supplied to the nervous system, as well as to other tissues. Cellular metabolism, as observed by Reichert, is reduced from 26 to 62 per cent. *Antipyrin, acetanilid* and kindred coal-tar products reduce the fits in some cases. They do so, however, as do opium and morphine, by causing constriction of the arterioles. The lowered metabolism induced by these agents is shown by the effects of large doses, *i.e.*, cyanosis.

The bromides and other depressants have their place in the treatment of epilepsy, however, as shown below, but only to counteract the excessive irritability of the general vasomotor center, while other measures are employed to antagonize the pathogenic elements in all idiopathic cases, *i.e.*, the poisons in the blood-stream.*

DECHLORINIZATION.—Withholding common salt from the diet of patients (used to render them more susceptible to the effects of the bromides) is not to be recommended, even though temporary benefit follow, this benefit being due to impairment of the osmotic properties of the blood and of the vital processes in which sodium fulfills an important rôle. Metabolism being retarded, nutrient materials accumulate in the blood and ultimately lead to additional disorders.*

The influence of common salt on osmosis is well known; Jacques Loeb[156] has shown that "the Nations of the blood as well as of the sea-water are essential for the maintenance of life-phenomena." Dechlorinization cannot, therefore, but deteriorate the body. This was illustrated in 30 cases carefully studied five months by J. Voisin, R. Voisin and Krantz.[157] At first the seizures were fewer, but the patients relapsed into their usual state. Marked anorexia appeared, the patients having to force themselves or be forced to take food. Then followed melancholia, confusion, hallucinations of sight, taste, etc., the patients fearing that they were being poisoned. In addition, there were dyspepsia, fatigue, lumbar and muscular pain. Schlöss[158] and others had already observed that under this treatment the patients became weaker. Conversely, Enriquez and Grenet[159] found that the addition of large doses of sodium chloride during four months diminished the intensity and number of attacks. C. H. Hughes[160] has, however, correctly emphasized the fallacy of dechlorinization as a therapeutic measure.

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* *Author's conclusion.*

[156] Jacques Loeb: Studies in General Physiol., Pt. II, p. 554, 1905.

[157] J. Voisin, R. Voisin and Krantz: Bull. et mém. de la Soc. méd. des hôp. de Paris, vol. xxi, p. 1215, 1904.

[158] Schlöss: Wiener klin. Woch., Bd. xiv, S. 1124, 1901.

[159] Enriques and Grenet: Arch. gén. de méd., vol. cxciii, p. 380, 1904.

[160] C. H. Hughes: Med. Fortnightly, Feb. 11, 1907.

MEASURES WHICH TEND TO PREVENT THE FORMATION OF TOXIC WASTES.—*Diet.*—In the light of the conclusions submitted in the foregoing pages, it becomes evident, in this connection, (1) that while any food ingested is converted into nucleo-proteid granules, we are dealing mainly with poisons formed during the breaking-down of worn-out living substances, *i.e.*, during catabolism; and (2) that these poisons form, owing to insufficiency of those constituents of the blood which carry on catabolism and destroy the toxic wastes in the blood* This, in turn, suggests as a fundamental principle, the imperative need of equipoise between these properties of the blood and the food-intake. In the majority of cases the latter is excessive, and the cellular elements are burdened with proteids which cannot be completely converted into eliminable products. The blood, therefore, is loaded with substances which irritate the vasomotor center and thus provoke the seizures.*

The practical indication is obvious, namely: to allow the patient only the quantity of food strictly necessary to the needs of the body. Indeed, neurologists of wide experience have found that the best results are obtained when the food consists mainly of cereals, milk, fruits and butter. Some include eggs, but others object to them. Meat, if allowed at all, should be strictly limited to the midday meal, and even then in small quantities. Alcohol, coffee and tea, should not be allowed.*

Fæcal stasis is a not infrequent cause, as barium meal x-ray examination shows. If *colonic flushing,* with the patient lying on his right side, fails to correct it, a *cæcostomy* permitting it is necessary. Any other focal disorder, whether situated in the tonsils, the nasopharynx, the nasal sinuses, the middle ear, the pelvic organs, etc., should be corrected.

As to dietetics Schlöss,[124] for instance, divided 16 cases into four groups: two of these were given meat *exclusively* six weeks, and a milk-and-vegetable diet during the succeeding six weeks. During the meat period the seizures were fewer than before; during the milk-and-vegetable period they increased. The reason for this suggests itself: the nucleo-proteid obtained from meat *only* was not equal to that of the milk and vegetables, while the nuclein intake was greater. As a result the phosphorus liberated during catabolism was relatively greater, and being added, on reaching the blood (via the lymphatics) to the phosphorus-laden nuclein in the auto-antitoxin, increased the plasma's proteolytic and therefore antitoxic activity. Indeed, Dana[102] gives glycerophosphates among other remedies, while B. Smith[103] has used pure phosphorus with advantage. The conclusion reached by some, that these and similar experiments indicate that patients should not be deprived of meat is erroneous, however, for it is because Schlöss's patients were placed on an *absolute* meat diet, that they were benefited. Meat given *besides* other foods cannot but aggravate the disease, in accord with the teachings of experience.

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* *Author's conclusion.*

[124] Schlöss: *Loc. cit.*

Alcohol and absinthe are recognized vasomotor stimulants and convulsivants, and abstinence therefrom, as shown by Forel and others, have proved curative. Fleury[104] cites several cases in which the cessation of alcohol and reduction of the diet alone very markedly reduced the number of seizures—the lapse in one instance being three years—although the treatment had not been modified. Tea was found by Haig,[105] and coffee by Marburg,[106] to aggravate the disease.

DRUGS WHICH TEND TO INCREASE THE DESTRUCTION OF TOXIC WASTES.—These agents all act by stimulating the test-organ, and therefore by increasing the blood's proteolytic activity.

Thyroid and Parathyroid Gland.—Thyroid gland is useful especially in young subjects (doubtless because gliosis is less apt to be present), owing to its direct action on the anterior pituitary body, as the physiological stimulant of this organ.* It not only increases, through the adrenals, the proportion of adrenoxidase in the blood, but also, and through this action, that of auto-antitoxin. All the antitoxic powers of the blood, phagocytic and plasmatic, being enhanced, the toxic wastes are more perfectly destroyed.* (See also p. 716, vol. i.)

In epilepsy, *small* doses are alone effective, since large doses, by too rapidly increasing the formation of adrenoxidase, cause excessive metabolic activity in all tissues and an augmentation of wastes.* The dose should not exceed 1 grain (0.065 gm.) of thyroid gland to begin with, and be slowly increased if need be, until not more than 3 grains (0.19 gm.) are taken three times daily, after meals. If extract of parathyroid is used, $^1/_{40}$ grain (0.0016 gm.) should be the initial dose, gradually increased to $^1/_{20}$ grain (0.0032 gm.).*

No depressants should be given at the same time, since they tend to antagonize the action of these extracts by reducing the sensibility of the test-organ. As the bromides, especially *sodium* or *strontium bromide,* only do so when given in full doses, however, 10 to 15 grains (0.64 to 1 gm.) may be given on retiring, to control the irritability of the vasomotor center, while the cause of this irritability is being counteracted by the thyroid extract.* The bromide salt may be combined with 5 grains (0.3 gm.) of *acetanilid.*

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* *Author's conclusion.*

[102] Dana: Med. Record, May 13, 1905.

[103] B. Smith: Texas Med. Jour., Aug., 1891.

[104] Fleury: Bull. gén. de thér., Jan. 23, 1900.

[105] Haig: Brain, vol. xix, p. 61, 1896.

[106] Marburg: Wiener klin. Rundschau, Bd. xiii, S. 257, 1899.

Under "Hæmophilia," the increase of oxidase caused by small doses (3 grains—0.19 gm.) *t.i.d.* of thyroid extract is graphically illustrated by tests in several cases treated by W. J. Taylor. That it can counteract convulsions has been emphasized mainly by experimental physiologists. "In some animals, as in most carnivora," says Chittenden,[197] "complete removal of the thyroid tissue is followed by a rapid development of symptoms indicating a marked irritation of the nervous and muscular systems, as manifested by tetanus, *epileptiform* convulsions, etc., and terminating in death." Thyroid extract, as is well known, cuts short these convulsions, the animal suffering in no way as long as it is administered. By stimulating the adrenal center, it enhances the production of oxidase and, therefore, that of auto-antitoxin. Browning[198] caused cessation of convulsions in three young epileptics, two of whom suffered from rickets and the third from "disturbed metabolism," by giving $^2/_3$ grain (0.043 gm.) doses of thyroid extract twice daily. He states that these cases "are due to or associated with disturbances in the general metabolism of the body" and refers to them as "pseudo-epilepsy." All cases of idiopathic epilepsy should be considered in the same light if the term "pseudo-epilepsy" were warranted at all, since, as we have seen, Pierce Clark and others ascribe the disease to "an accumulation of waste-products." Browning's cases were *bona fide* cases of epilepsy, and what they do teach is that small doses of thyroid extract are alone indicated. These, however, as my own observations have shown, must be *very gradually* increased according to the effect on the patient. I usually begin with one grain (0.065 gm.) at each meal, giving a small dose of sodium bromide on retiring at first, if necessary, and gradually reducing the dose, until none is given at all. Some cases are benefited by larger doses of thyroid. Thus, in a case treated by a colleague, under my supervision, the nurse, through a misinterpretation of instructions, doubled the dose; the result was considerable improvement. In adults, however, as it did in cases reported by Clarke[199] and Bourneville,[200] it failed to arrest the seizures. In fact, in the last-named neurologist's cases, it increased the number of seizures. But the cause of this is evident: the extract was administered in full doses, and excessive metabolism was produced, causing an excessive production of wastes. As the cases were adults, diffuse gliosis may have been present, recovery being then impracticable. It is in young subjects that the best results are obtained with thyroid extract used as above. Professor Osborne, of Yale,[201] wrote recently: "I have now on my records a number of cases of epilepsy treated successfully with thyroid. My attention was first drawn to the use of this preparation in epilepsy by several cases occuring in women at the time of the menopause, the attacks showing a suggestive periodicity.... I found that I could control and prevent the epileptic attacks as well with thyroid as could be done with bromides, and with much better results to the system."

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* *Author's conclusion.*

[197] Chittenden: Trans. Congr. Amer. Phys. and Surgs., vol. iv, p. 87, 1898.

[198] Browning: Jour. of Nerv. and Mental Dis., Oct., 1902.

[199] Clarke: Amer. Jour. of Insanity, Oct., 1895.

[200] Bourneville: Progrès méd., vol. xxiv, p. 20, 1896.

[201] Osborne: Jour. Amer. Med. Assoc., Nov. 3, 1906.

Sodium Salicylate and Salicin.—The salicylates increase very actively the elimination of urea and uric acid, by actively stimulating the adrenal center. Moreover, they excite abnormally the sympathetic center and cause constriction of the peripheral arterioles and, therefore, reduce the convulsions by limiting the cerebro-spinal hyperæmia. In adults 15 grains (1 gm.) of sodium salicylate or salicin 5 grains (0.3 gm.) may be given three times daily, giving a small dose (10 grains—0.64 gm.) sodium bromide at bedtime.

The salicylates have been recommended by Haig[322] and used with advantage, but with potassium iodide. William Pepper likewise used the salicylates with success. A number of cases have been reported in which it reduced the number of seizures. W. J. Vincent,[323] in a severe and carefully studied case, in which all familiar remedial measures had been tried, arrested the seizures (nine months' test) with salicin 5 grains (0.3 gm.) three, then five times, in the twenty-four hours. Other cases were benefited.

Other drugs which tend to enhance catabolism and the destruction of wastes are *digitalis* and *strophanthus, adonis vernalis, iodide of sodium,* and *biniodide of mercury.* Their actual value will only be ascertained when given alone, *i.e.*, reserving depressants for the night. For the latter purpose *bromipin,* a brominized oil of sesamum, has been recommended in lieu of the bromides; *antipyrin, acetanilid,* and *urethan* likewise. The centers seem to lose their sensitiveness to remedies sooner in epilepsy than in other diseases. An *alkaline laxative,* preferably the citrate of magnesia, every other week, aids materially all the foregoing measures.*

TREATMENT OF STATUS EPILEPTICUS.—In this condition the main cause of the paroxysms is the intense vascular pressure, caused by a more or less great accumulation of toxic wastes. Here the bromides are of value when injected subcutaneously in the back, just below the angle of the scapula, 30 grains (2 gms.) of *sodium bromide* dissolved in one ounce (28 gms.) of sterile water being used repeatedly if need be. *Amyl nitrite* inhalations, which cause temporary paresis of the vasomotor center and relaxation of all the arteries, while useful to abort ordinary attacks when used during the aura, are seldom effective in status, but used in addition to the bromide injections, prove efficient. *Blood-letting* has been highly recommended; *hypodermoclysis* suggests itself as a valuable measure used immediately after the bleeding to aid in the elimination, through the marked diuresis it provokes, the elimination of waste-products.

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* *Author's conclusion.*

[322] Haig: "Uric Acid as a Factor in the Causation of Disease," London, 1892.

[323] W. J. Vincent: Jour. of Mental Sci., Apr., 1904.

The use of sodium bromide as above was found highly useful in the Mass. Hospital for Epileptics by Morton and Hodskins.[334] They also administer prophylatic injections of 20 minims each (in all 12 grains) when two seizures occur in succession. Chloroform is sometimes recommended, but Pierce Clark[335] states that chloroform should never be used during the sleep or stupor stage of the access, as it may cause coma and even death. According to Bondurant,[336] the best single remedy for status epilepticus is blood-letting.

TREATMENT OF JACKSONIAN AND REFLEX EPILEPSY.—When the lesion in Jacksonian epilepsy can be clearly located, the sooner operative procedures are resorted to the better. As a period of improvement follows almost any procedure, prudence in predicting a cure is desirable.

All cases of epilepsy should undergo a very careful examination lest any organ of special sense be the source of reflex seizures. Any abnormal condition should, if possible, be corrected, even if it happen not to be the spasmogenic factor, since it always tends to aggravate the disease.

EPILEPTOID DISORDERS.

INFANTILE ECLAMPSIA OR CONVULSIONS.—The seizures of this disorder, which resemble those of epilepsy, are ascribable to a similar morbid process,* autotoxins being, as a rule, derived from the gastro-intestinal canal. They may also be due to general hypocatabolism, however, as is observed in children suffering from rickets; or, they may occur as an intercurrent symptom of acute infections, where they are caused by the inability of the adrenal system to cope successfully with the aggregate of detritus, wastes, etc., which appear in the blood under such conditions.* The paroxysms may be brought on by reflex action, through dentition, precisely, as we have seen under Epilepsy, as is the case under the influence of nasal growths, phimosis, etc., *i.e.*, through irritation of the corresponding centers in the posterior pituitary.*

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* *Author's conclusion.*

[334] Morton and Hodskins: Boston Med. and Surg. Jour., June 15, 1905.

[335] Pierce Clark: Pediatrics, Aug. 15, 1897.

[336] Bondurant: Amer. Jour. of Insanity, July, 1894.

The medicinal *treatment* of infantile convulsions is, on the whole, similar to that of the disorders studied in this chapter. An important feature, however, is the careful search for conditions, such as the teething, phimosis, rickets, etc., and their elimination as pathogenic factors. The convulsive, *i.e.*, epileptic, habit may be developed in children left untreated, since repeated hyperæmia of the neuroglia* may provoke a gliosis and place the case beyond our aid.

PUERPERAL ECLAMPSIA.

SYNONYMS.—*Puerperal Convulsions; Child-bed Fits.*

Definition.—Puerperal eclampsia, an acute disorder of pregnancy and parturition characterized by periodical convulsions, is due to an accumulation of toxic wastes in the blood, owing to inability of the adrenal system to convert the excess of wastes due to the presence of the fœtus, into benign and eliminable end-products. As these toxic wastes provoke inordinate vascular tension, an excess of blood is driven into all capillaries, including those of the spinal system and cortex. Both the latter being thus rendered hyperexcitable, a convulsion occurs when this hyperexcitability is suddenly increased by the appearance in the blood of an excess of auto-antitoxin, the result, in turn, of a sudden resumption of defensive activity by the adrenal system when the blood becomes sufficiently toxic to enforce it. The convulsion lasts until the toxic wastes are converted more or less efficiently into harmless and eliminable end-products.**

Symptoms and Pathology.—The symptomatology of puerperal eclampsia, as regards the convulsions, closely resembles that of epilepsy. It may be divided into three stages: (1) the invasion, (2) a short period of tonic spasm, and (3) the period of clonic convulsions.

The period of *invasion* is generally attended (besides other phenomena reviewed under "Etiology and Pathogenesis") with a severe frontal headache, sudden flashes, more or less blurred vision, vertigo, and mental torpor or excitement. The temperature gradually rises and the pulse and heart-beat become steadily stronger. Nausea and vomiting may also occur, the patient complaining of pain in the epigastrium. More or less severe chills mark the approach of the seizure in most cases.

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* *Author's conclusion.*

** *Author's definition.*

The *tonic* spasm may, however, occur suddenly, *i.e.*, without warning, and is usually very brief. The eyes remain wide-open and staring, the pupils being dilated, the face is very pale and consciousness is lost. The spasm consists in pronation and supination of the forearms, the fingers being tightly closed around the thumbs, and rigidity of the legs. The head and mouth are drawn to one side, generally the right, the breath is "held" through arrested action of the respiratory muscles, and opisthotonos may occur. The tonic spasm may appear alone, and recur, thus constituting the only form of convulsion witnessed. As a rule, however, it lapses into the clonic seizure.

The onset of the *clonic* stage is marked by a change in the appearance of the patient, the face becoming deeply congested, tumefied, then cyanotic. The eyeballs, fixed before, now move rapidly from side to side, the lids closing and opening rapidly, the pupils, from dilated, becoming contracted. The muscles of the face and jaws are violently contracted, the tongue being sometimes severely bitten; the patient foams at the mouth, and the head is tossed or rolled from side to side with great rapidity and violence. All the extremities are thrown around vigorously and rapidly flexed and extended, the back being arched in opisthotonos or to the side. The respiration is markedly impeded and often stertorous; the pulse and heart at first beat slowly and forcibly, the veins of the neck being turgid and distended, but later on the cardiac action may become irregular. The temperature in most cases rises to 104° F. (40° C.); in some it may reach much higher, *i.e.*, 110° F. (43.3° C.).

After a period varying from one-half to three minutes the paroxysm loses its violence, and the patient falls into a coma or a deep sleep. Sometimes a new paroxysm recurs while the patient is still comatose, and is followed by others in more or less rapid succession. Rarely, the patient dies during the first coma. In favorable cases, the seizures become less frequent or cease immediately after delivery.

Etiology and Pathogenesis.—The convulsions are due, as in epilepsy, to irritation, by blood-poisons, of the vasomotor and sympathetic centers. All the vessels of the body being violently contracted, a wave of blood is forced into all capillaries, including the cellular elements and neuroglia of the cerebro-spinal system.[*] The activity of the cortex as a sensory organ being suddenly enhanced, a flood of impulses—of the voluntary type—is transmitted to every portion of the spinal system and the seizure occurs.[*]

The arterial pressure is so intense that the capillaries are sometimes found ruptured, hæmorrhagic lesions being found even in the placenta. This violent hyperæmia is the cause of the great fatality of eclampsia to the infant.[*]

The kinship between epilepsy and eclampsia is so close that some authors, Osthoff and Lantos,[307] for instance, consider the latter as an acute form of epilepsy. Others, again, compare it to hystero-epilepsy. Oliver[308] reported a fatal case of epilepsy in a young puerperal patient with no antecedent history of the disease.

That a marked and widespread vascular constriction and general capillary hyperæmia are present has been conclusively demonstrated. Not only does the facial congestion, the engorged veins of the surface, betoken the presence of these conditions, but as observed by Lubarsch,[309] multiple hæmorrhages are to be found in every part of the body: the liver, kidneys, stomach, large intestine, endocardium, lungs, etc., and in the pia mater and cortex. Schmorl[310] also found punctiform hæmorrhage of meninges and cortex, and moreover of the central ganglia. Similar lesions, as to the cortex, were noted by Leusden,[311] who also observed many ruptured capillaries, the blood flowing in the surrounding tissues, forming clots. Massen[312] found the veins of various regions completely thrombosed, and also "considerable dilatation of the cerebral capillaries," the blood having been forced into them, doubtless by the constricted arteries. All organs showed hæmorrhagic lesions of some kind. Cassaet and Chambrelent[313] found hæmorrhagic lesions in the still-born infants similar to those of the mother, and ascribe to this cause the great mortality of infants in eclamptics. The hepatic lesions of eclampsia have also received considerable attention from Jürgens,[314] Klebs, Pilliet,[315] Bouffe de St. Blaise and others, since all found in this organ hæmorrhagic and embolic foci. Finally, Blumreich and Zuntz[316] found experimentally that the brain of pregnant animals was much more susceptible to irritation than that of non-pregnant ones.

We thus have ample testimony to the effect that, as in epilepsy, the cortex is violently congested, and if in the latter disease this can provoke convulsions, there is no ground for doubt that the case is the same in puerperal eclampsia. The connection with the vasomotor center is well expressed by Herz:[317] "Even slightly toxic products in the blood of women in childbed are sufficient to irritate the vasomotor centers, which are then in a condition of increased excitability." Finally, Krönig[218] found by means of the Riva-Rocci sphygmomanometer that the blood-pressure was very high, especially in post-partum eclampsias, an observation confirmed by H. Richardson.[219] Vaquez[220] wrote recently that none of the theories in vogue in regard to the etiology of eclampsia took into account the main and essential feature, viz., arterial hypertension. He had evidently overlooked the abundant evidence to that effect in literature.

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[*] *Author's conclusion.*

[307] Lantos: Archiv f. Gynaek., Bd. xxxii, S. 364, 1888.

[308] Oliver: Lancet, May 26, 1894.

[309] Lubarsch: Corr. f. schweizer Aerzte, Bd. xxi, S. 255, 1891.

[310] Schmorl: "Pathologisch-Anatomische Unter. u. Puerperal Eklampsia," Leipzig, 1893.

[311] Leusden: Virchow's Archiv, Bd. cxlii, S. 1, 1896.

[312] Massen: Ann. de gynécol. et d'obstét., vol. xl, p. 227, 1893.

[313] Cassaet and Chambrelent: Revue médico-chir. des mal. des Femmes, vol. xvii, p. 660, 1896.

[314] Jürgens: Berl. klin. Woch., Bd. xxiii, S. 374, 1886.

[315] Pilliet: Nouvelles arch. d'obstét. et de gynéc., vol. v, p. 600, 1900.

[316] Blumreich and Zuntz: Arch. f. Gynäk., Bd. lxv, S. 737, 1902.

[317] Herz: Wiener med. Woch., Bd. l, S. 113, 174, 227, 284, 326, 381, 1900.

The spasmogenic poisons are intermediate products of tissue catabolism which accumulate in the mother's blood when her auto-protective mechanism, the adrenal system, is inefficient, *i.e.*, functionally hypoactive.*

During pregnancy the mother's blood becomes increasingly laden with waste-products, those of the developing fœtus being added to her own. To protect her organism, her adrenal system, including, of course, the thyroid apparatus, becomes increasingly active, owing to the exciting action of these products on the test-organ,* to insure destruction of all wastes as soon as they are found.* When the adrenal system does not become sufficiently active to enhance adequately the blood's antitoxic properties—including phagocytosis—the toxic wastes are allowed to accumulate in the blood* in sufficient quantities to provoke convulsions, *i.e.*, the eclamptic seizures.

Williamson, of Johns Hopkins,[221] in his recently published textbook says: "Up to the present time satisfactory proof has not been adduced in support of the bacterial nature of eclampsia, nor does it seem likely to be forthcoming," and he considers it probable that the "morbid process is caused by some as yet unknown poisonous substance circulating in the blood which may give rise to lesions of varying intensity in the several organs." The lesions to which he refers include those I have ascribed to excessive hyperæmia in all organs, the result of irritation of the general vasomotor center. After alluding to the fact that it was Bouchard who opened up the field of auto-intoxication, he writes: "Rivière, in 1888, was the first to put forward the theory that eclampsia was an auto-intoxication resulting from the heaping up of some substance in the system." Tarnier and Chambrelent[222] and others found the toxicity of the blood considerably increased, but this question is still *sub judice*. Nevertheless the kinship with epilepsy again suggests itself, since Ludwig and Savor[223] and Hofmann[224] regard carbonic acid as the spasmogenic agent, while Sälli[225] ascribes this rôle to some "intermediate products from the proteid molecule." I would again suggest that several poisons should be incriminated, since the nervous system also supplies intermediate wastes under such conditions differing from those of other tissues. In a recent comprehensive biochemical study of the question, however, Zweifel[326] found that the eclamptic seizure followed the accumulation of lactic acid—which he ascribes to deficient oxygenation—in the blood, and that after the seizures this acid had disappeared.

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* *Author's conclusion.*

[218] Krönig: Verh. d. deut. Gesellsch. f. Gynäk., Bd. ix, S. 312, 1901.

[219] Richardson: Amer. Medicine, Sept. 12, 1903.

[220] Vaquez: Semaine méd., vol. xxvii, p. 121, 1907.

[221] Williamson: "Obstetrics," p. 708, 1903.

[222] Tarnier and Chambrelent: Annales de gynéc. et d'obstét., vol. xxxviii, 321, 1892.

[223] Ludwig and Savor: Monats. f. Geb. u. Gyn., Bd. i, S. 447, 1895.

[224] Hofmann: Centralbl. f. inn. Med., July 16, 1898.

[225] Sälli: Berl. klin. Woch., Oct. 22, 1900.

That the mother's auto-protective resources are developed coincidently with the growth of the fœtus through a corresponding augmentation of the functional activity of the adrenal system is fully sustained by experimental evidence. As to the *pituitary body*, L. Comte[327] found microscopically that, during pregnancy, the *anterior* pituitary was hypertrophied; it was also very much heavier and larger. This was confirmed by Launois and Mulon[328] in two instances, one of the parturients having died eclamptic. They found, moreover, a marked increase of the cellular elements. In a more recent work[329] Prof. Launois reiterates his previous conclusion that in pregnancy the anterior lobe is in a state of marked "hyperactivity".

Lang,[330] in a series of 133 cases of pregnancy, found the *thyroid* enlarged in 108, the organ beginning to enlarge about the fifth month. This increase in volume ceased, however, if thyroid extract was administered, and began again when the extract was withdrawn. On the other hand, Verstraeten and Vanderlinden[331] and Nicholson[332] having concluded that in eclampsia nitrogenous metabolism is impaired, owing to insufficiency of the thyroid, the latter author tried thyroid extract and found that it counteracted the morbid symptoms—a fact repeatedly confirmed since, as shown under "Treatment."

As to the *parathyroids*, Vassale[333] reviewed recently his own labors and those of Pepere, Zanfrognini and others, which showed lesions of these organs after death from eclampsia; of Zanfrognini, Erdheim, Thaler and Adler, which showed that parathyroid insufficiency beginning during the last three months of pregnancy caused grave (experimental) eclampsia. In two out of three dogs in which the parathyroids had been removed, Vassale was able to prevent eclampsia by giving large quantities of parathyroid extract orally. Frommer[334] has confirmed the general trend of these views.

That stimulation of the *adrenals* by the pituitary body increases the antitoxic power of the blood, we have seen under "Epilepsy." The need of such a function in eclampsia is self-evident in view of the fact that Massin[335] found that at the end of pregnancy the blood contains an abundance of "partially oxidized products or leucomaines." It is only a question whether this function—carried on by the adrenal system—is equal to the occasion. As in epilepsy, also, the eclamptic stage is an effort of protective functions to destroy the poison. Indeed, Emery[336] observed that a polynuclear leucocytosis—the identical cells which we have seen furnish the blood its nucleo-proteid granules—occurs at the onset of the fever, and Kollmann[337] found a large increase of fibrinogen, a substance rich in nucleo-proteid, in the blood of eclamptics.

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[326] Zweifel: Arch. f. Gynäk., Bd. lxxvi, S. 537, 1905.

[327] Comte: Thèse de Doctorat de Lausanne, 1898.

[328] Launois and Mulon: Ann. de gynéc. et d'obstét., 2 série, vol. i, p. 2, 1904.

[329] Launois: Thèse de la Faculté des Sciences de Paris, 1904.

[330] Lang: Zeit. f. Geburts. u. Gyn., Bd. xl, S. 34, 1899.

[331] Verstraeten and Vanderlinden: Ann. de la Soc. de méd. de Gand, vol. lxxvi, p. 72, 1897.

[332] Nicholson: Jour. of Obstet. and Gynec. for Brit. Empire, July, 1902.

[333] Vassale: Gaz. degli Ospedali, Aug. 5, 1906.

[334] Frommer: Monats. f. Geb. u. Gynäk., Bd. xxiv, S. 748, 1906.

[335] Massin: Centralbl. f. Gynäk., Bd. xix, S. 1105, 1895.

[336] Emery: Practitioner, Mar., 1905.

[337] Kollmann: Centralbl. f. Gynäk., Bd. xxi, S. 341, 1897.

Albuminuria is an index to the degree of vasoconstriction present.* When the vasoconstriction becomes excessive, there is added to the albuminuria, transudation of the albuminous portion of the blood (the serum) through the engorged capillaries, and œdema of the feet, legs, external genitals and face appears.* In marked cases, the trunk and the internal organs, especially the lungs, may likewise become œdematous.

The albuminuria of pregnancy, *when moderate,* is not due to a general constriction caused by the action of poisons on the general vasomotor center.* We have seen that it is the result of excessive vital activity in the muscular coats of the arteries, owing to the unusually stimulating properties of the blood supplied to them through the vasa vasorum and that it is purely mechanical.* Though albuminuria is not due to nephritis, renal irritation may be evoked by the inordinate work imposed upon the kidney. Moderate albuminuria alone is not a threatening condition, therefore; while moderate albuminuria *plus* renal casts may ultimately prove to be.* Albuminuria with œdema points to a marked vascular constriction which may become pathological.*

Lantos[238] found albuminuria in 60 per cent. of 600 newly delivered women, in over 70 per cent. of 268 primiparæ, and over 50 per cent. of 332 multiparæ, and concluded that it has no pathological significance. Palmer[239] also found albuminuria in about 50 per cent. of pregnant women examined at the Cincinnati Hospital. Pajot,[240] nearly twenty years ago, laid stress on the fact that many women who were highly albuminuric do not have eclampsia.

Willamson,[241] referring to the older view that nephritis was the fundamental cause of albuminuria, states that it was "gradually abandoned when it was found that only a small proportion of the women had eclampsia." This shows that the two phenomena are distinct entities. Indeed, as emphasized by Bar,[242] a normal action of the kidney does not prevent a fatal ending, while conversely, as shown by Van der Velde,[243] albuminuria may be absent notwithstanding the presence of marked renal disease. Nor do, as noted by Saft[244] and others, casts and albumin maintain a corresponding ratio. Just as the waste-products, as already stated, increase coincidently with the growth of the embryo, so did Saft, in his study of 707 cases, find that when albuminuria occurred, it was between the thirtieth and thirty-second weeks, and that while it was apt to become very considerable as the puerperium approached, it receded during the first days following labor. The general vasoconstriction is likewise shown by the facts, pointed out by Nicholson,[325] that during pregnancy the right side of the heart is dilated, while the left side acts as though it were hypertrophied. Obviously, as he suggests, this is due to widespread and extreme vasoconstriction, a condition linked with the albuminuria of pregnancy by Allbutt, the blood being jammed into the venous system. The dilation of the right heart affords an idea of the intense centrifugal pressure to which the capillary system is submitted, and the familiar fact that the serum of the blood normally traverses the walls of the capillaries to penetrate the lymph spaces, indicates how it may traverse mechanically the renal filter, or invade the tissues and render them œdematous. Indeed, in a recent paper, Mynlieff[326] found marked intrarenal distention, sufficient to cause stasis at times, and limited only by the resistance of the capsule.

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* *Author's conclusion.*

[238] Lantos: *Loc. cit.*

[239] Palmer: Jour. Med. Coll. of Ohio, May, 1891.

[240] Pajot: Med. Press and Circular, Aug. 8, 1882.

[241] Williamson: *Loc. cit.*

[242] Bar: Bull. médical, vol. xiv, p. 77, 1900.

[243] Cited by Williamson. *Loc. cit.*

[244] Saft: Archiv f. Gynäk., Bd. li, S. 207, 1896.

Although Charpentier[327] regards eclampsia without albuminuria as exceptional, he, Schroeder and Ingerslev[328] found numerous cases in literature in which it was absent. But this is readily accounted for by the fact that in some cases the brunt of the irritation is borne by the sympathetic centers. The arterioles being constricted, the circulation of the kidneys is inhibited as it is elsewhere, the pressure being only sufficient to sustain renal activity. In fact, the inhibition may exceed this limit: in 42 cases reported by T. K. Holmes,[329] the bladder contained no urine in 5 instances, although these cases had all been œdematous, while the only case in which albumin was absent, œdema was likewise absent. This case—in which the vasoconstriction was evidently not intense—had only one convulsion. Three cases attended with anasarca, and "solid" urine as to albuminuria, proved fatal.

The relative excretion of urea is an index to the proportion of the toxic waste-products that are present in the blood. The addition of fœtal products of metabolism to those of the mother necessarily involving an increase of them in the maternal blood, a corresponding increase in the urea excreted should occur. In eclampsia it is markedly reduced and the severity of a given case corresponds with the urea excreted, while improvement coincides with a material increase in the amount eliminated.

Butte[330] observed that when in eclampsia the proportion of urea excreted was normal, death usually followed: while recovery ensued as a rule, when it was doubled. Marx[331] has long emphasised the fact that "urea is always found markedly diminished in the so-called pure toxæmias of pregnancy" and that "the amount of urea excreted always goes hand in hand with the condition of the patient." E. P. Davis[332] emphasizes the same fact and states that although urea is not itself a poison, diminution in the quantity excreted indicates that toxins are being retained. Jewett[333] regards a marked falling off as of grave import. Hélouin[334] found that in eclampsia the nitrogen eliminated in the form of urea was markedly lower than during normal pregnancy. Whitney and Clapp[illegible] confirmed this fact experimentally and clinically. Williams states that while, during an eclamptic attack, there is nearly always an abundance of albumin, often blood and tube-casts, the termination of the convulsions is marked, in favorable cases, by a rapid increase in the amount of urine and urea, together with a decrease in the amount of albumin."

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[325] Nicholson: Jour. of Obstet. and Gynec. for Brit. Empire, Jan., 1905.

[326] Mynlieff: Centralbl. f. Gynäk., Bd. xxix, S. 392, 1905.

[327] Charpentier: Bull. de l'Acad. de méd. de Paris, 2 série, vol. xxix, pp. 22, 54, 1893.

[328] Cited by Williamson: *Loc. cit.*

[329] T. K. Holmes: Med. Age, Feb. 10, 1896.

[330] Butte: Ann. de la policlin. de Paris, vol. iii, p. 164, 1893.

[331] Marx: Sajous's "Analytical Cyclo. of Pract. Med.," vol. v, p. 375, 1900; Med. Exam. and Pract., Mar., 1904.

[332] E. P. Davis: Amer. Gyn. and Obstet., July, 1899.

[333] Jewett: Brooklyn Med. Jour., Aug., 1899.

[334] Hélouin: Thèse de Paris, 1890.

Treatment.—MEASURES CALCULATED TO PREVENT ECLAMPTIC SEIZURES.—In view of the foregoing evidence, the importance of frequent examination of the urine is self-evident: at least once a month during the first six months and every other week thereafter, the patient being instructed to notify her accoucheur should headache, disturbance of vision, œdema, or jaundice appear—all symptoms of beginning toxæmia. The urine passed in the twenty-four hours, which will probably be found highly colored and scanty, should be measured, and the total output of albumin and urea estimated by Esbach's albuminometer and Doremus's ureometer.

Although the addition of the fœtal wastes to those of the mother suggests that an excess of urea should be found, obstetricians are content with a normal output of urea (20 to 24 grams daily) even if a slight amount of albumin be present. Considerable albumin and a diminution of the urea excreted, however, betoken danger, and the patient should at once be restricted to *milk* (which serves both as food and diuretic), two quarts at least to be taken in the twenty-four hours, and all the water she can drink. When this does not procure the desired result, a decrease of albumin, a rise of urea-ratio and free diuresis, the daily use of *saline purgative* and *hot-pack* or *sweat-bath* should be resorted to.

An *exclusive milk diet* is recommended by Williamson and other American obstetricians, and by most French authorities, Charpentier, Tarnier and others. Charpentier,[illegible] in fact, to avoid all risk, orders it as soon as the urine contains the slightest trace of albumin, which would mean that about 50 per cent. of pregnant women should at one time or another be submitted to it. Féré[illegible] and Tarnier (whose experience has been extensive) had never seen at the time of their report a case of eclampsia in a patient who had subsisted for eight days on an absolute milk diet. As Féré observes, it does not always counteract the albuminuria or the œdema, but it averts toxic symptoms. This is accounted for by the conclusion I have submitted that the two former symptoms, when not marked, are not necessarily pathological, their persistence denoting that the patient's blood is rich in adrenoxidase.

[illegible] Whitney and Clapp: Amer. Gynecology. Aug., [illegible].
[illegible] Charpentier: Arch. de tocologie et de gynéc., vol. xx, p. [illegible], [illegible].
[illegible] Féré: L'obstétrique, vol. i, p. [illegible], [illegible].

If no improvement occur in the excretory phenomena and the headache and visual disturbances persist; or if drowsiness, hebetude and other symptoms previously enumerated as denoting irritation of the vascular centers appear, the likelihood that an attack of eclampsia is near at hand is very great. When this stage is reached, obstetricians usually induce premature labor, the life of the unborn child being sacrificed. According to my interpretation of the pathogenesis of the convulsions, other means are available, besides those just outlined, to prevent the attack of eclampsia.

The use of *saline solution* is indicated before as well as during the eclamptic period, since it is known to enhance the antitoxic activity of the blood by increasing its fluidity and its osmotic properties.[*] When the absolute milk diet is not increasing the excretion of urea, therefore, sodium chloride should be added to the milk in the proportion of 50 grains (3.3 gms.) to the pint,[*] the patient being directed to drink water at stated intervals. Often in these cases, there is fæcal retention, notwithstanding daily evacuations. *Rectal irrigation* with large quantities (one to two gallons) of warm (110° F., 43.3° C.) saline solution is very valuable in all cases.

The experimental researches of Von Fodor, Blumenthal, Calabrese, Löwy and Richter and others have conclusively demonstrated that the antitoxic powers of the blood are inhibited by a diminution of its salts, while Jacques Loeb has shown that sodium chloride was essential to the life of the cell. Its beneficial effect during the eclamptic stage, even in apparently hopeless cases, is well known. As stated by Allen,[***] "it is impossible to appreciate its advantages unless one has watched its results." The taste of milk is improved rather than impaired by the quantity of salt mentioned. The effects of thyroid extract are given below. The use of high rectal injections, especially of saline solution, is generally recognized.

If these measures do not procure the desired result, the patient should remain in bed to reduce the proportion of sarcolactic acid eliminated by the muscular tissues into the lymph and blood, thus counteracting the only remaining poison-producing factor, namely, muscular exertion.[*] The absolute milk diet being continued, *thyroid gland* should be given in doses of 3 to 5 grain (0.2 to 0.3 gm.) doses every three hours, the object being to stimulate the adrenal mechanism and increase the antitoxic activity of the blood.* *Oxygen* inhalations are indicated in this connection, to hasten the conversion of the adrenal secretion into adrenoxidase.*

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[*] *Author's conclusion.*

[***] Allen: Amer. Jour. of Obstet., May, 1899.

The advisability of avoiding muscular exertion is well shown by the experiments of Mossaglia,[illegible] who found that dogs deprived of some of their parathyroids had typical convulsions after being fatigued. He emphasizes the fact that a woman threatened with eclampsia is more prone to an attack after being fatigued. We have seen that Vassale observed marked eclampsia during pregnancy in dogs deprived of their parathyroids, and that large doses of parathyroid arrested the attack.

Nicholson[illegible] introduced this treatment on the well-grounded plea, based on Lang's observation that the thyroid was enlarged, and his own that during eclampsia this phenomenon did not occur, that a deficient supply of iodothyrin entailed a corresponding inadequate destruction of nitrogenous wastes. Although he believed that the antitoxic action of the thyroid secretion was direct and that the poison acted directly on the blood-vessels also—both untenable conclusions—the fact remains that the object—destruction of the spasmogenic poisons—was attained in the four cases reported. The doses ranged from 5 to 10 grains (0.3 to 0.6 gm.). In the first case, the seizures had begun; in the second there was slight general œdema and albuminuria; in the third the general œdema included the face, the urine was nearly solid, there was headache and dimness of vision. The fourth case was similar. Nicholson's observations have been confirmed by several obstetricians—but all after the convulsions had begun. Frühinsholz and Jeandelize[illegible] likewise advised the use of thyroid extract.

The inhalation of oxygen has been found of value even without thyroid extract; hence its probable efficiency with an increase of adrenal secretion in the blood-stream.

Simultaneously, if need be, the irritability of the general vasomotor center may be reduced by using drugs which are known to prove beneficial during the convulsions, and which are, therefore, all the more indicated in the pre-eclamptic stage.* *Veratrum viride* is one of these; by inducing relaxation of all the arteries of the body it causes accumulation of the blood in the large central vessels, and by thus diminishing the cerebral hyperæmia tends to prevent the impending seizure. It may be given in 20 to 30 drop doses of the tincture (1905 U. S. P.) every two hours until the pulse becomes softer and slower, but larger doses are required in threatening cases to obtain this result. The physiological action of the *bromides* and *chloral* is similar to that of veratrum, we have seen, but their action is more uncertain.

The use of veratrum viride does not prevent that of thyroid extract, since each drug acts on a different center. The former should not be used hypodermically, however, in the pre-eclamptic period, since the reflex irritation produced by the needle and fluid may precipitate a seizure.

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* *Author's conclusion.*

[illegible] Mossaglia: Gazz. degli Ospedali, Sept. 2, 1906.

[illegible] Nicholson: Brit. Med. Jour., Oct. 11, 1902.

[illegible] Frühinsholz and Jeandelize: Presse médicale, Oct. 25, 1902.

Wood, we have seen, says that veratrum viride bleeds the patient into his own vessels—a desirable effect under present conditions. Thayer[illegible] laid stress on the fact that during puerperal convulsions, a "peculiar tolerance" of viride existed, officinal doses having no effect. This is due to the great erethism of the vasomotor center; hence the need of full doses in the pre-eclamptic period. Edgar[illegible] considers it "the most certain remedy at our command for controlling the spasms temporarily, or even permanently." Norris, Hirst,[illegible] Jewett[illegible] and other obstetricians of large experience recommend it highly in convulsions. That it should be as useful to *prevent* convulsions, while the thyroid extract is causing destruction of the toxic wastes in the blood, is obvious.

Measures Calculated to Arrest the Eclamptic Seizures.—If, notwithstanding the foregoing measures, eclampsia occurs, efforts to eliminate the poison and arrest the convulsions should even now be made before sacrificing the child by emptying the uterus. The irritability of the vasomotor center is best controlled, we have seen, by means of *veratrum viride,* 40 minims (3.6 gm.) of the tincture (1905 U. S. P.) may now be given hypodermically. Pending the vasodilating influence of this remedy, the convulsions may be held in check, if absolutely necessary, by means of a few whiffs of *chloroform* (an undesirable agent, since it irritates the vasomotor center) freely diluted with air. *Hypodermoclysis* should then be resorted to, one pint of saline solution at 110° F. (43.3° C.) being injected slowly beneath each breast. This may be repeated if necessary. Many experienced obstetricians practice *venesection* before using the saline solution, and find it of material aid, especially in plethoric or cyanotic women. To promote diaphoresis, the *hot pack* is generally recommended, and is much safer than pilocarpine. *Thyroid gland* is also indicated during this stage, but in full doses. *Iodine,* in large doses, may serve to replace thyroid extract if the latter is not available. (See also p. 784.)

The cases in which Norris found veratrum viride most useful were those with a full, rapid and high-tension pulse. Cotret[illegible] injects 20 drops, and the same quantity in 30 minutes if the pulse is not reduced.

[illegible] Thayer: Boston Med. and Surg. Jour., Apr. 1, 1897.
[illegible] Edgar: Therap. Gaz., Aug. 15, 1901.
[illegible] Hirst: *Ibid.*
[illegible] Jewett: Amer. Med. Digest, Feb. 15, [illegible]
[illegible] Cotret: Rev. médicale du Canada, vol. vi, pp. 215, 220, 1902.

In one case he thus injected 400 drops, saving the case. E. P. Davis injects 40 minims (1905 U. S. P.) every hour until it falls below 90 and its tension is decidedly lessened. Hirst, who gives 60 to 80 drops (1905 U. S. P.) as the first dose, has seen it reduce the pulse to 60 in a few minutes; as long as it remained at that rate no convulsions occurred. Lapthorn Smith[267] obtained subsidence of the blood-tension with 20 to 25 minims after other familiar remedies and even blood-letting had failed.

The beneficial influence of saline solution is well illustrated by the fact that in the Glasgow Maternity the mortality, according to Jardine,[268] has been reduced from 47 per cent. to 17 per cent. since this measure has been introduced. One drachm of sodium chloride to the pint of water at 110° F. (43.3° C.) is the solution employed, the site of the infusion being covered with towels wrung out of hot water.

Besides the pre-eclamptic cases treated by Nicholson, cases in which the seizures had developed and in which thyroid or parathyroid extract was successfully employed, have been reported by Macnab,[269] Baldowsky,[270] Vassale[271] and others, the last-named author having used later,[272] and with equal success, parathyroid extract.

Thyroid extract in large doses is recommended by Nicholson, Fothergill, Sturmer[273] and Lobenstine.[274] The latter gave it in 20-grain doses (1.3 gm.) per rectum several times in the twenty-four hours.

Acting upon my suggestion[275] that iodine should prove efficient in such cases, Somers[276] used doses sufficient to produce iodism of a preparation containing a large proportion of free iodine sucessfully. This indicates that this halogen can be used advantageously when fresh thyroid extract cannot be obtained. I prefer the iodides of sodium and potassium in large doses. It may also be administered per rectum with saline solution.

Morphine injections are advocated by some, but the benefit produced is an artificial one; the arterioles being constricted, the peripheral circulation is hampered and the cortical hyperæmia is reduced. The arteries are dilated behind their arterioles, by the accumulated blood; hence, the belief that it causes vasodilation. The arterioles of the skin and kidneys being likewise constricted, their excretory functions are inhibited.* It should not be used, therefore, when the kidneys are at all diseased. It is far more efficacious, as shown below, when administered with chloral hydrate.

Francis[277] lost two cases out of five under morphine. Conversely, Fitzgerald[278] reports five cases, of which two, treated by chloroform and delivery, died, while the three others, in which morphine was used without delivery, lived. Veit[579] also recommends morphine, but when renal disease is not present—in accord with Tyson,[580] Reynolds Wilson[581] and others. Hoig[582] uses it only when there is free diuresis. He rightly avoids it also during the comatose state between seizures. Edward P. Davis[583] advises against its use, especially in large doses.

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* *Author's conclusion.*

[267] Lapthorn Smith: Montreal Medical Journal, Jan., 1902.

[268] Jardine: Edinburgh Med. Jour., July, 1902.

[269] Macnab: Jour. of Obstet. and Gynec. of Brit. Empire, Nov., 1904.

[270] Baldowsky: Vratch, vol. xi, 1904.

[271] Vassale: Riv. Crit. di Clin. Med., Mar. 4, 1904.

[272] Vassale: Arch. Ital. di Biol., vol. xliii, p. 177, 1905.

[273] Sturmer: Brit. Med. Jour., Apr. 16, 1904.

[274] Lobenstine: Bul. N. Y. Lying-in Hosp., Dec., 1905.

[275] Sajous: Jour. Amer. Med. Assoc., Feb. 4, 1905.

[276] Somers: Western Med. Review, June, 1904.

[277] Francis: Brit. Med. Jour., Jan. 11, 1902.

[278] Fitzgerald: *Ibid.*, Nov. 24, 1900.

Chloral acts much as does veratrum viride, but, unlike the latter, it reduces the sensitiveness of the adrenal center besides controlling the irritability of the vasomotor center. While relieving the cortical hyperæmia, therefore, it tends to reduce the antitoxic properties of the blood.* The *bromides* have a similar action, when the doses are sufficiently large to control the convulsions.* As a temporary resource, however, chloral may be used advantageously when well diluted with water, by the mouth, or by rectal injections when the patient cannot swallow.

While the majority of European obstetricians consider chloral too depressing, Goodell, Hirst, Charpentier and other experienced observers advocate its use: Frazer[584] administered it per rectum, 1 drachm (4 gm.) being used for each enema, in 40 cases, and lost but two. Commandeur[585] contends that its rectal use is defective: it is not well retained and absorption is uncertain. Orally, when each 15 grains given is dissolved in at least 4 ounces (120 gms.) of water, it is well borne, and completely absorbed. Hallowes[586] reported four cases in which the injection per rectum of 60 grains (4 gms.) in 1 ounce (28 gms.) of water gave prompt relief.

Morphine and Chloral.—Combined, these two agents are far more useful than when given alone. Morphine being capable of stimulating both the adrenal center and the sympathetic center, it offsets the untoward action of chloral on the former, but not its depressing action on the vasomotor center. The chloral, therefore, tends to deplete the brain, *i.e.*, the cortex, of its excess of blood, while the morphine by constricting the arterioles, still further reduces the quantity of blood admitted to the cerebral capillaries.*

This accounts for the results recorded by Stroganoff,[587] viz., a mortality of 5.4 per cent. out of 92 cases observed by him. He injects 1/6 grain (0.01 gm.) morphine, and repeats the dose in one hour or earlier if the patient is restless. Two hours later he gives chloral per rectum, 30 to 45 grains (2 to 3 gms.) in aqueous solution, and repeats it at intervals of 4, 6, and 8 hours, unless the patient be resting quietly. Chloroform is used exceptionally—only in severe convulsions, pending the action of the morphine and chloral. The rectal and subcutaneous use of saline solution is deemed an important feature of the treatment. The author *did not have to induce labor in a single instance.*

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* *Author's conclusion.*

[579] Veit: Festsch. f. C. Rüge, 1896.

[580] Tyson: Gaillard's Med. Jour., Aug., 1891.

[581] Reynolds Wilson: Annals of Gynec. and Pediat., May, 1892.

[582] Hoig: Canadian Practitioner, July, 1900.

[583] E. P. Davis: Therap. Gaz., Dec. 15, 1899.

[584] Cited by Robbins: Amer. Lancet, Jan., 1898.

[585] Commandeur: Semaine méd., vol. xxii, p. 328, 1902.

[586] Hallowes: Lancet, July 13, 1901.

[587] Stroganoff: Vratch, Sept. 16, 1900.

If the foregoing measures prove unavailing, the uterus should be emptied. The precautions resorted to in epilepsy to prevent wounding of the tongue, etc., during the convulsions, are, of course, as applicable in eclampsia.

RABIES.

SYNONYMS.—*Hydrophobia; Lyssa.*

Definition.—Rabies, a disorder characterized by violent tonic spasms with, in some instances, clonic convulsions, is the terminal stage of an infection by a specific virus which causes progressive paralysis of the test-organ. The functions of the adrenal system becoming gradually weaker, toxic wastes accumulate in the blood to a sufficient degree, after weeks or months, to cause a marked increase of vascular tension. As an excess of blood is thus driven into all capillaries, including the cerebro-spinal nervous elements, these are rendered hyperexcitable. The spasms occur when this hyperexcitability is suddenly enhanced by the appearance in the blood of considerable auto-antitoxin, due to a defensive reaction of the adrenal system evoked by the blood when it becomes sufficiently toxic to irritate violently the test-organ notwithstanding the paralyzing influence of the virus.*

Lyssophobia or *Pseudo-rabies*, a morbid fear of hydrophobia in persons who have been bitten by animals supposed to be rabid, consists of a group of symptoms resembling true rabies, but including manifestations, such as attempts to bite, bark, etc., which are popularly thought to belong to rabies.

Symptoms and Pathology.—After a period of *incubation* varying from one week to three months, and in rare cases extending beyond this length of time, the *premonitory symptoms* appear. At first they resemble those of other diseases, irritability, anorexia, insomnia, depression and general malaise. Slight headache and rigors with some stiffness and even pain in the muscles of the neck, back and shoulder and arms are frequently complained of. The tongue is coated, the breath offensive, and the pupil is dilated. There may be slight fever, but in most cases the temperature is normal, and hypothermia is occasionally present. If the patient attributes his condition to the bite, brooding over its consequences may lead to melancholia and influence greatly the symptomatology of the second period of the disease. The wound, usually healed soon after the receipt of the injury, may be the seat of darting pains, become inflamed along, perhaps, with neighboring lymphatic glands.

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* *Author's definition.*

Although occasionally rabies occurs long after the injury, most cases in which it appears beyond four months are not sustained by control inoculations. Bradford[illegible] states that "the incubation period in the human subject lies between 20 to 60 days, and it is exceedingly rare to have it appear after 3 months, and 6-months' incubation is practically unknown." As to the presence of low temperature, Sir Thomas Smith[illegible] observed a case which on admission had a temperature of 95° F. (35.50° C.) and a pulse of 56. Anders[illegible] observed two cases in which the dread of the disease after bites resulted in persistent melancholia.

The *spasmodic* stage is initiated by the symptoms due to excessive reflex irritability of the pharynx, larynx and œsophagus, the act of swallowing provoking reflex spasm of their muscles, and therefore intense dyspnœa owing to closure of the glottis. At first the difficulty is surmounted, but the spasms finally become so intense that they inspire extreme terror, and the sight of water, by suggesting the act of deglutition, is sufficient to bring on a distressing seizure. Hence the term "hydrophobia," a misnomer, since it is the spasm that is feared. The patient is nevertheless extremely thirsty and sometimes controls himself sufficiently to drink; milk is taken more readily than water under these conditions, especially if given in a covered vessel. In some cases, deglutition is impossible and the liquid regurgitates by the mouth and nose. Even the saliva, which in rabies is viscid, tenacious and secreted in greatly increased quantity, causes spasm when swallowed, and is expectorated, sometimes in its normal state, sometimes mixed with froth, owing to the churning it receives in the mouth—the so-called "frothing at the mouth."

The mucous membranes are not alone in a state of exalted irritability; as in tetanus, there is general hyperæsthesia of the skin, and the special senses become so acute that a slight

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[illegible] Bradford: Lancet, Mar. 3, 1900.
[illegible] Sir Thomas Smith: Practitioner, Jan., 1898.
[illegible] Anders: "Practice of Med.," seventh edition, p. [illegible], 1905.

touch, a mere draught, a noise, etc., suffice to provoke a paroxysm. The orificial tissues, those of the anus for instance, are quite as sensitive, even rectal feeding causing spasm. Nor are the muscles of the upper respiratory and alimentary tracts alone involved in these seizures; the entire muscular system, including both the voluntary and involuntary muscles, may, as in tetanus or even in epilepsy, undergo violent contraction. The muscles of mastication are, in most cases, alternately locked and relaxed, causing the snapping which popular imagination has interpreted as efforts to bite. In truth, the patient, who is relatively quiet and able to speak rationally (at least in the earlier part of the convulsive stage), during the interval between the spasms is usually solicitous about those who minister to his wants. Rolling of the eyes and head, throwing of the limbs from side to side, etc., as in epilepsy, are also witnessed in some instances.

As the case proceeds, the mental excitement increases, the patient talking incoherently. This often lapses into the so-called "furious" stage, during which the patient is subject to waves of maniacal delirium, as it were, attended with delusions and hallucinations of a frightful nature. This coincides with an elevation of the temperature, reaching in some cases 105° F. (40.5° C.), a bounding, tense and rapid pulse, flushed face and eyes, and sometimes cyanosis. The pulse may become small and irregular during a spasm developed during this stage—a danger signal of oncoming cardiac (coronary) inhibition* and sometimes of immediate death.* Glycosuria and albuminuria are also observed during this stage.

The period of excitement finally passes into one of comparative quietude. The patient is then able to swallow with less trouble and may be thought to be recovering. But it is in reality the onset of the lethal or *paralytic period;* the cardiac action becomes weak and irregular, and the respiration shallow and rapid. The patient then gradually lapses into unconsciousness and coma, dying by syncope or in the midst of a terminal tetanic spasm. Death usually occurs within the four days following the onset of the convulsive period, but occasionally the patient lasts much longer.

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* *Author's conclusion.*

In rare cases, usually in neurotic or debilitated subjects or after multiple lacerations, the phenomena are all of the paralytic type. After the usual premonitory symptoms, dysphagia and attacks of spasmodic dyspnœa appear, soon followed by coldness, anæsthesia and torpor of the extremities, especially the lower. Paralysis follows and gradually becomes general, the lethal course described above then progressing rapidly.

The resemblance of rabies to tetanus is not only very marked, but tetanus is sometimes attended with distinct hydrophobic symptoms. In two cases reported by Roberts[illegible] and Van Spanje,[illegible] both in gardeners, in which infection occurred through slight wounds of the face from pointed sticks, the phenomena were clearly those of rabies. Anders and Morgan[illegible] refer to a case of tetanus reported by J. W. Ward, in which the diagnosis of hydrophobia was maintained several days. The paralytic form of rabies, that observed also in inoculated guinea-pigs and other animals, the rabbit, mouse, etc., is another point of similarity with tetanus. As to death occurring beyond the usual four days, Sweeney and Denny[illegible] refer to a case in which death occurred on the fourteenth day following the onset of the rabic symptoms. These authors correctly interpret what a study of a large number of carefully described cases indicates, when they remark: "The exaggerated picture of rabies in the mind of the laity and of physicians who have carelessly read text-books on the subject is never met with in actual practice. The barking, biting, crawling on all-fours and other extravagant symptoms belong rather to the spurious or hysterical type of the disease." In a case of the latter kind described by Fabricius,[illegible] the patient tried to bite, but he was clearly reproducing his conception of what a rabid man should do—though in the midst of a sharp attack of alcoholic delirium from which he promptly recovered.

Etiology and Pathogenesis.—Rabies is due to the presence in the blood of a poison which violently irritates the vasomotor and sympathetic centers.* The resulting intense constriction of all arteries causes all the capillaries of the body to become correspondingly engorged by the blood forced into them, and the spinal (and in some cases the cortical) cells being thus rendered hyperæmic, they become, as in tetanus, excessively irritable.* As the sensory terminals of the peripheral mucous membranes and skin are also rendered hypersensitive through hyperæmia of their capillaries, the least irritation of the surface provokes a violent reflex spasm.*

The pharynx, larynx and œsophagus are the first to react, because it is to this region that an external irritant is applied when ingesting fluids or food. Irritation applied elsewhere, the surface, the anal aperture, etc., likewise produces spasm in these structures and in them only at first because they are nearest to the seat of the general centers primarily irritated, those in the pituitary body.*

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* *Author's conclusion.*

[illegible] Roberts: Lancet, July 11, 1891.

[illegible] Van Spanje: Nederlandsch Tijdschrift voor Geneeskunde, vol. xxvii, p. 397, 1891.

[illegible] Anders and Morgan: Jour. Amer. Med. Assoc., July 29, 1905.

[illegible] Sweeney and Denny: Northwestern Lancet, Apr. 1, 1898.

[illegible] Fabricius: Med. Record, Dec. 28, 1895.

The presence of marked vascular engorgement has been emphasized by a large number of observers. Van Gehuchten and Nélis,[356] for instance, found "everywhere in the nervous system a vascular dilatation" and in some, "general thrombosis of the small veins with an excessive perivascular infiltration." Babès[357] had previously laid stress on this condition. In a case controlled by inoculations in rabbits by Ravenel, and reported by Krauss,[358] Wadsworth found "severe congestion of the cerebral and spinal meninges, numerous punctate hæmorrhages in the spinal cord, and a rupture of the pleura." In another case proved by inoculations, J. Douglas found "the brain moderately congested, also the pons and medulla and especially the floor of the fourth ventricle." Tchernischeff also found small hæmorrhages in the floor of the fourth ventricle, besides intense hyperæmia of the white and gray substance of the cord, etc. Finally Anglade and Choireaux,[359] in a series of comparative experiments, found that intense hyperæmia appeared early and simultaneously in the blood-vessels and neuroglia (which, as I have pointed out, are neural capillaries) and that these lesions were not specific to rabies, but were observed in other disorders, including epilepsy. As to the throat and œsophagus being the seat of spasm earlier than other structures being due to the proximity of the pituitary body, Bradford[360] refers to the fact that "a wound of the face, inasmuch as it is near the central nervous system, is for that reason more dangerous." The *sensorium commune* of the posterior pituitary is essentially the central motor system under these conditions, as I have shown.

The primary cause of rabies is a specific virus, the nature of which has not so far been determined, introduced into the bitten tissues with the saliva of the rabid animal. The development of the disease, *i.e.,* the spasmodic period, which usually ends fatally, depends upon the antitoxic efficiency of the bitten subject's blood:—if this is adequate, as is the case in about 84 per cent. of individuals bitten by rabid animals, the virus is soon destroyed and rabies does not develop; if it is not, the virus indirectly initiates the disease.* In the latter case the interval between the time of infection and the appearance of rabies constitutes the period of incubation, and the duration of this period is therefore proportionate with the antitoxic properties of the blood.*

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* *Author's conclusion.*
[356] Van Gehuchten and Nélis: Presse médicale, vol. vii, p. 113, 1900.
[357] Babès: Wiener med. Blätter, Bd. xviii, S. 665, 1895.
[358] Krauss: Phila. Med. Jour., Jan. 26, 1901.
[359] Anglade and Choireaux: Progrès méd., May 31, 1902.
[360] Bradford: *Loc. cit.*

During the incubation the virus is likewise destroyed by the blood's auto-antitoxin, but only in the arteries, arterioles and capillaries that contain leucocytes, because these cells supply the proteolytic ferment and nuclein which, with oxidase, form the auto-antitoxin.* As, conversely, adrenoxidase-laden plasma devoid of leucocytes circulates in the nervous elements, *i.e.*, the axis-cylinders, dendrites, etc., the neuroglia and neuroglia-cells and all other neural capillaries, what virus penetrates into them is not destroyed and it accumulates therein.* Hence the fact that the virus is found in the nervous system and not in the blood.*

The penetration of the virus into the nervous system is a normal result when, in accord with my views, all nervous elements contain plasma derived from the general circulation.

The minute quantity of virus that is capable of causing rabies, and its presence in relatively large quantities in the nervous system and some glands, and many other facts, involve the need of some organism such as the bacillus tetani that is capable of secreting toxins. Bradford[illegible] concludes a review of the evidence to this effect with the statement that although "it cannot be said that the identity of the organisms of rabies has been clearly established" . . . . "there are many strong arguments in favor of the disease being of microbic origin." He regards Leblanc's statistics as to the proportion of persons bitten by rabid animals, and which place it at 16 per cent., as probably the most accurate.

Duboué[illegible] is credited by Pasteur[illegible] with the statement that the virus "propagates itself insensibly even to the central nervous system along the nervous fibers"—the first suggestion to this effect confirmed by Roux and many others. Pasteur, Burdach, Catani, Di Vestea and Zagari[illegible] and others also found that the intra-nervous inoculation was the more effective in producing the disease experimentally.

The attenuation of the virus obtained by Pasteur by inoculating monkeys in succession has not so far been explained: it is readily accounted for by the presence of auto-antitoxin—the proteolytic triad—in the blood of these animals.* Nor has the manner in which the prophylactic effects of the Pasteur treatment are produced been shown: As I have previously pointed out,[illegible] "the extract of desiccated cord injected raises the anterior pituitary body's functions to their normal standard and sustains them until all danger is past." In other words, it stimulates the test-organ and the blood of the exposed subject is rendered sufficiently rich in antitoxin to insure the destruction of the virus. That it is upon the functional efficiency of the adrenal system, therefore, that the development of rabies depends, is obvious.

The time finally comes, however—weeks in some, months in others—when the gradual decline of catabolic activity due to this inhibition of the adreno-thyroid mechanism by the virus, provokes so great an accumulation of toxic wastes in the blood that notwithstanding its torpor, the test-organ is caused to react.* The adrenals and the thyroid apparatus being stimulated, the blood receives a large excess of adrenoxidase and, as a result, a corresponding surplus of trypsin and leucocytes, the source of nucleo-proteid granules.* The thyroid apparatus being also and simultaneously activated, thyroidase accumulates in the blood along with the phagocytes produced during the leucocytosis.* On the whole, the blood suddenly becomes laden with auto-antitoxin and germicidal cells, to destroy the virus if possible.* If this supreme effort—*which marks an advanced stage of the disease*—fails,* the paralyzing influence of the virus continues and death soon follows.

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* *Author's conclusion.*

[illegible] Bradford: *Loc. cit.*

[illegible] Duboué: "De la physiol. path. et du traitement rationnel de la rage," Paris, 1879.

[illegible] Pasteur: C. r. de l'Acad. de méd., Jan. 18, 1881.

[illegible] Di Vestea and Zagari: Giornale interne delle sci. mediche, vol. xi, p. 81, 1889.

[illegible] Sajous: Phila. Med. Jour., Mar. 7, 1903.

The reaction to the accumulation of these toxic wastes, in other words, is the spasmodic period of the disease, the fully developed rabies.* This disease differs only from tetanus in that the toxæmia is more profound, and in that the virus tends, owing to its paralyzing influence on the nerve-centers, to limit the convulsions of the extremities. The paralytic phase of the disease coincides with the time when, the virus having obtained the upper hand, it paralyzes the central nervous system.*

The true action of the virus is clearly illustrated by the so-called "paralytic" form of rabies first described by Van Swieten, in 1771. Anders[illegible] refers to this disease as follows: "In man there is a paralytic form of rabies, but it is rare as compared with the delirious or psychic type. Thirty cases have been reported by Gamaléia, and it is apt to follow *deep* and *multiple* bites. The paralysis begins near the part bitten and spreads until it becomes general, finally involving the respiratory centers." If the virus is a direct spasmogenic agent, why should the large quantities introduced fail to produce spasm? Experimental inoculation points in the same direction. In rabbits, guinea-pigs and other herbivora, the paralytic form is the prevailing one, as is well known. In rabbits, Di Vestea and Zagari observed that "from the fifth day after infection, the *temperature* rises with light febrile movements, to fall *suddenly* with the coming on of the first paralytic symptoms until the resulting death." We have in the febrile state the reaction of the adreno-thyroid center, but the convulsions witnessed in carnivora fail to appear. This obviously shows that the spasms are in reality grafted upon the true disease.

Prophylactic Treatment.—If an extremity is bitten, a ligature should be placed immediately above the lesion to encourage bleeding and reduce the amount of virus distributed by the afferent vessels. The wounds and all their recesses should then be carefully cleansed and then asepticized with *hydrogen peroxide,* or a 5-per-cent. solution of *potassium permanganate.* Cauterization is of distinct value; *nitrate of silver* has been highly recommended, and pure *carbolic acid* likewise. Experiments have shown, however, that opening of the wound under anæsthesia and thorough cauterization with fuming *nitric acid* gave the best results.

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* *Author's conclusion.*

[illegible] Anders: "Practice of Medicine," p. [illegible], 1905.

Gowers[507] states that "it is doubtful whether the disease ever occurs if a stick of nitrate of silver is immediately plunged into a wound." Youatt[508] considers nitrate of silver sufficient; having obtained a failure in a single case out of 400. F. Cabot[509] conducted a series of comparative experiments to determine which was the best cauterizing agent, and concluded that fuming nitric acid was the most effectual substance for cauterization, and that it was of great value if employed within the first 24 hours. J. C. Vaughan[510] states that a couple of drops suffice in the wound made by a tooth. The slough soon separates, leaving a clean wound which heals readily.

AGENTS WHICH INCREASE THE BACTERICIDAL AND ANTITOXIC PROPERTIES OF THE BLOOD.—Pasteur's *preventive inoculations,* we have seen, owe their virtue to their stimulating influence upon the adreno-thyroid center; they enhance, therefore, the efficiency of the body's auto-protective functions.* The earlier the treatment is begun the better; as soon as the wounds are treated as above and dressed, the patient should be sent to the nearest Pasteur Institute. The dog should not be killed, since the non-development of rabies in the animal within a few days affords proof that the bites were benign.

Pasteur Institutes have been established in New York, 313 West Twenty-third Street; Baltimore, corner of Saratoga and Calvert Streets; Chicago, 228 Dearborn Avenue.

Other prophylactic measures have been suggested. Bouchard used successfully in animals a fluid obtained by filtration from rabies-infected nerve-tissue. Babès, in collaboration with Lepp, Cerchez and Talasecu,[511] likewise conferred immunity in animals with a serum of inoculated dogs—a result also reached by Tizzoni, in collaboration with Schwartz[512] and Centanni,[513] with sera obtained from rabbits and sheep. These agents have failed to gain the confidence of the profession. The serum recommended by Tizzoni is far more powerful than that of Babès;

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* *Author's conclusion.*

[507] Gowers: "Diseases of the Nervous System," vol. ii, second edition, p. 925, 1893.

[508] Cited by Tyson: "Practice of Medicine," p. 187, 1905.

[509] Cabot: Med. News, Mar. 18, 1899.

[510] J. C. Vaughan: Indian Med. Gaz., Aug., 1896.

[511] Babès: Ann. de l'Inst. Pasteur, vol. iii, p. 384, 1889; vol. v, p. 637, 1891; vol. viii, p. 434, 1894.

[512] Tizzoni: Riforma Médica, 1892.

[513] Centanni: Atti della Reale Accad. dell Sci. dell Inst. di Bologna, Feb. 10, 1893.

but the fact that it is obtained from herbivora suggests the reason for this: being poor in antitoxin, the blood of these animals is rich in virus. Babès's serum obtained from Carnivora is less dangerous, the virulence of the virus being mitigated by the potent antitoxin found in the blood of such animals; but in the Pasteur method the material used at first is obtained from spinal cords in which the virus has been rendered inactive, and it is only when (from my viewpoint) the blood has thus been rendered richer in antitoxin that the virulent cords are used. It is, therefore, the least dangerous method of its kind.

P. B. Hadley[334] wrote recently: "Of 1608 cases treated at the New York Pasteur Institute previous to 1901, only four gave symptoms of disorders which could be traced directly to the treatment. Three had a partial paralysis of the lower limbs, lasting from one to three weeks; one patient had facial paralysis lasting four weeks. All of these cases made uneventful recoveries. The anti-rabic vaccinations may cause a slight nervousness among neurasthenic and hysterical persons; but these disturbances are never serious and are extremely rare. As to actual fatalities, records show that out of 1367 persons treated at the New York Pasteur Institute in the years 1890 to 1900 there were nine deaths, a mortality of 0.65 per cent. In 1900, from January to September, at the New York Pasteur Institute, there were 921 cases treated and two deaths, representing a mortality of 0.1 per cent. From October 1, 1904, to October 1, 1906, there were 486 treatments with one death, representing a mortality of 0.206 per cent. Reports from other institutes show about the same results; and finally, a compilation of statistics from the reports of the Pasteur Institute of Paris for the last twenty years shows that, out of 20,000 treatments, the mortality rate has been 0.25 per cent."

Unfortunately not every one can bear the direct and traveling expenses which the Pasteur treatment involves, especially in this country, where the Pasteur Institutes are few. The need of equally active prophylactic agents, offering also the advantages of being within the reach of any physician, is, therefore, very great.

When the spasmodic or second stage of rabies is allowed to develop, the patient is practically doomed, his auto-protective functions being virtually paralyzed.* *It is upon the efficiency of the preventive measures, therefore, that his life depends.** Both the virus and the toxic wastes being destroyed by the blood's auto-antitoxin, and *thyroid extract* causing a rapid increase of the latter, this remedy not only meets the conditions of a powerful prophylactic, but being available everywhere, its use may be begun at once; 3 grains (0.19 gm.) should be given every two hours, in adults.* As its untoward effects are due to vasoconstriction of the cardiac coronaries, which, when excessive, inhibits the heart,* the action of the remedy should be watched; and if the pulse become weak or dyspnœa appear, the dose should be reduced. After the second day, 5 grains (0.3 gm.) three times a day after meals suffice to sustain the antitoxic activity of the blood above the normal standard—above, in other words, the efficiency required to destroy the virus.*

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* *Author's conclusion.*

[334] P. B. Hadley: Providence Med. Jour., Jan., 1907.

The pathological kinship between rabies and tetanus, and the remarkable effects of thyroid extract in the tetanic convulsions that follow extirpation of the thyroid, distinctly point to this remedy as valuable in this connection. We have seen that the proportion of adrenoxidase can be gauged by the coagulation time and that thyroid extract rapidly increases the blood's coagulating properties, and that the proportion of adrenoxidase betokens a corresponding increase of antitoxin. Strychnine, we have seen, likewise enhances the formation of oxidase. Fleet-Surgeon Thorpe[555] recently ascertained that a remedy used successfully by the Chinese not only as a prophylactic, but as a cure in the early stages of developed cases, was a species of strychnos seed which, on analysis, gave the characteristic tests of brucine and strychnine, the former being in excess. In India, an insect closely related to the ordinary *cantharis vesicatoria* is used with success, according to Kotak.[556] This coincides with the Russian method, *i.e.*, hypodermic injections of potassium cantharidate, 1/[illegible] to 1/[illegible] grain (0.001 to 0.002 gm.), or tincture of cantharides, 10 minims (0.6 gm.) three times daily. Garlic is extensively used by the Arabs. All these agents are powerful adreno-thyroid stimulants—though all much less so than thyroid extract.

Moreover, a number of observers have found that *in vitro* the blood destroyed the virus in from 15 to 22 hours; but, as previously stated, such experiments have but little value, the adrenoxidase being promptly reduced by the phosphorus-laden nucleo-proteid in the plasma.

Among other agents which powerfully stimulate the adrenal center and enhance, therefore, the production of auto-antitoxin, are the *iodides*, the *biniodide of mercury*, and *digitalis*. The first named most nearly approximates thyroid extract as a prophylactic.* Less active as adrenal stimulants are *strychnine* and *quinine;* but by stimulating, in addition, the vasomotor and motor centers, and causing general vasoconstriction, they cause accumulation of the blood in the cutaneous capillaries, including those around the injured area, where the auto-antitoxin can best destroy the virus.* *Cocaine* suggests itself as an efficient protective agent in this connection, but the danger of initiating the cocaine habit should be borne in mind.*

The rapidity with which the hydrochlorate of quinine drives the blood towards the periphery and thus overcomes a localized accumulation of pathogenic organisms, their toxins and detritus, is well shown by its effect in the treatment of furuncle. Even if the boil is one of a long series, 3 grains (0.18 gm.) every three hours cause a flushed face, tinnitus, headache, etc., after eight or ten doses. When this stage is reached, the furuncle rapidly recedes. In some of my cases it began to do so after the sixth dose. This method should not be used in subjects in which arteriosclerosis is likely to be present. Smaller doses, say 2 grains (0.13 gm.) with 1 grain (0.065 gm.) of thyroid, given in the same manner, soon increase the proportion of oxidase in the blood without, in the average case, causing either tinnitus or the other phenomena mentioned. Cocaine might be used in the manner I have indicated under "Coca and Cocaine."

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* *Author's conclusion.*

[555] Thorpe: Lancet, May 14, 1904.

[556] Kotak: Indian Med. Record, Feb. 16, 1898.

Heat is a powerful prophylactic. By exposing the bitten extremity of the body to a vapor bath until free sweating occurs, blood is not only drawn to the surface and the injured area, but the proteolytic activity of its antitoxin is greatly enhanced.* The chances of insuring destruction of the virus are, therefore, correspondingly increased.* Its immediate use should be supplemented by another sitting, after the blood's antitoxin will have been augmented by means of thyroid extract or one of the above-named adrenal stimulants.*

We have seen that the proteolytic activity of ferments in auto-antitoxin is greatly increased by a marked rise of temperature. The use of the vapor-bath was recommended by Buisson, and has been used successfully in many instances. The unsatisfactory explanations given as to its physiological action, and its use by laymen, have caused the method to fall into disrepute. But Shepard[837] has collected a number of *bona fide* instances in which it had been used successfully by physicians not only as a preventive, but also in fully developed cases. My interpretation of its physiological action accounts for these results.

Irrespective of the Pasteur method, the foregoing measures appear to me ample to prevent the development of rabies in subjects bitten by rabid animals.

As in tetanus, the *diet* is an important feature of the morbid process.* The fact that the spasmodic stage does not, as a rule, occur in some herbivora, points to the need of avoiding the accumulation of toxic wastes derived from animal foods, *i.e.*, of prohibiting the use of meat until all danger is past.* The patient should also drink water freely in order to facilitate the elimination of end-products of metabolism.

Treatment of Developed Rabies.—In the light of my views, the measures recommended *for the corresponding stage of tetanus* are as applicable in rabies. The reader is therefore referred to page 1446.

If used promptly, *i.e.*, during the premonitory stage, these measures, supplemented by others described below, may turn the tide in favor of the patient. As the saliva in cases of developed rabies has been proved to be infectious, the attendants should carefully cover any abrasion that they may have on the hands or face.

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* *Author's conclusion.*

[837] Shepard: Jour. Amer. Med. Assoc., Oct. 23, 1897.

As *mercury* and *iodide* stimulate most actively the adrenal center, it is apparent that *thyroid gland* must be effective in rabies as it is in tetany, but in larger doses, since the virus tends to paralyze the test-organ.* Either of the former agents may be used when the thyroid extract cannot be obtained.*

Again, inasmuch as the spasmogenic agent is in rabies, as it is in tetanus, an autotoxin, the *antitetanic serum* meets the needs of the situation. It should be used in large doses, however, and injected into the median basilic vein.* Many of the successful cases reported had been bled; but as *bleeding* alone provokes tetany by diminishing the volume of fluid in which the spasmogenic autotoxin is dissolved, it should be promptly supplemented by intravenous injections of *saline solution*.

That spontaneous cure may occur has been shown experimentally by Högyes.[528] Out of 159 animals in which the virus was injected in fatal doses, recovery occurred in 13 instances in which Pasteur preventive inoculations were used. The seven animals treated by the Pasteur method recovered. Laveran[529] and Chantemesse[530] have likewise reported *bona fide* cases which led them to conclude that rabies was not necessarily fatal. Although the many cases cured during the earlier portion of the nineteenth century suggest the possibility of errors in diagnosis, the fact remains that, according to Lucas Benham,[531] *mercury* held a prominent place in the 50 instances of recovery cited. Illingworth[532] recommends intramuscular injections of the biniodide of mercury with sodium iodide (1 to 50).

The use of saline solution was praised by Magendie many years ago. The reasons adduced in favor of Baccelli's *carbolic acid* treatment obtain as well in rabies, and there is reason to believe that it would prove very efficacious in this disease, since, as observed by Blasi and Travali, the virus is easily destroyed by antiseptics, especially creolin. Moreover, the oral use of a solution of carbolic acid has been highly recommended by Déclat and Peyroulx[533] as a prophylactic.

The *vapor-bath* has occasionally given good results even when the convulsive period was well advanced. During the premonitory stage, the procedure may be carried out readily, but when the convulsions have begun, it is sometimes necessary to fasten the patient to the bed or chair.

Interpreted from my standpoint, as previously stated, the proteolytic, *i.e.*, antitoxic, property of the blood is greatly enhanced by heat. Kellogg[534] states that "the effect of the vapor-bath upon the body temperature is very profound, the rectal temperature rising in the course of 20 or 30 minutes to the extent of 3 to 4 degrees." Again, "the axillary temperature rises more rapidly and to a higher point than the rectal temperature." Obviously the bath inhibits for a time the elimination of heat and thus provokes a temporary fever, which, like all febrile processes, serves to destroy the pathogenic element.*

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* *Author's conclusion.*

[528] Högyes: Orvosi Hetilap, vol. v, p. 36, 1889.

[529] Laveran: Semaine médicale, vol. xi, p. 130, 1891.

[530] Chantemesse: *Ibid.*, vol. xi, p. 139, 1891.

[531] Lucas Benham: Lancet, Mar. 1 to 15, 1890.

[532] Illingworth: "Abortive Treatment," p. 19, 1888.

[533] Déclat and Peyroulx: "L'acide phénique," Paris, 1874.

[534] Kellogg: "Rational Hydrotherapy," p. 703, 1901.

Buisson's own case hardly warrants the diagnosis of rabies; but instances of unmistakable rabies in which the Buisson method was successfully employed were observed by Leon Petit, Hermance, Cameron, Gray and others.[illegible] Some of these used the Turkish bath; but as Kellogg says: "The temperature of both the rectum and the axilla rises much more quickly in the vapor-bath than in the Turkish or dry hot air bath." Others apply the cold-sheet after the vapor-bath; but this imposes upon the patient an unnecessary hardship, and drives the blood into the deeper vessels, including neural capillaries. The longer blood is kept in the peripheral capillaries, the longer, of course, the virus and the spasmogenic autotoxins will be exposed to the blood's proteolytic action.

MEASURES WHICH CONTROL SPASM.—Here, again, the measures recommended for the corresponding stage of tetanus are indicated, but only when their use is necessary to arrest the spasms or reduce their violence while the blood's auto-antitoxin, augmented by either of the remedies mentioned, is counteracting the paralyzing influence of the virus.* The latter is in reality the death-dealing agent in rabies, and to destroy it should be our aim.* The bromides, chloral and kindred drugs being themselves paralysants,* *amyl nitrite* inhalations are preferable, though the former cannot be dispensed with, as a rule.

A ten-per-cent. solution of *cocaine hydrochlorate* sprayed, not into the mouth, where it is wasted owing to great amount of saliva secreted, but into the nasal cavities as far back as possible, suggests itself as a valuable adjuvant to prevent paroxysms.* It trickles down the post-nasal cavities and the pharyngeal wall and by anæsthetizing the superficial sensory terminals of the latter, inhibits the intense reflex irritability so manifest in this region.*

Osler[illegible] recommends the local application of cocaine, but the quantity of saliva in the mouth and the irritability of the pharynx render this measure very difficult. Free spraying into the nose while the patient is in the recumbent position is readily accomplished.

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* *Author's conclusion.*

[illegible] Cited by Shepard: *Loc. cit.*

[illegible] Osler: "Practice of Medicine," third edition, p. 229, 1898.

CHAPTER XXV.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

PAIN-CAUSING DISORDERS DUE TO HYPOACTIVITY OF THE ADRENAL SYSTEM.

Balfour[1] wrote a few years ago, referring to the pathogenesis of gout: "With all our increased accuracy in details, it does not appear that our ideas of what gout really is are any clearer or any better defined than those of our forefathers." If anything, the obscurity surrounding this question may be said to have become greater, more recent investigations having overthrown those which ten years ago seemed of great promise. Even these modern products of the laboratory evidently rest upon a very weak foundation, for Graham Lusk in a recently published work[2] (1906), closes a review of purin metabolism in gout with the suggestive remark that "present-day doctrines concerning metabolism in gout may shortly become entirely obsolete through new and far-reaching discoveries." In truth, the labor that physiological chemists have devoted to this subject, though fruitful as to valuable experimental facts, has remained sterile as to final results, and will continue to do so because they persist in ignoring the cardinal functions of the adrenal secretions in metabolism and in the life process itself, where their work has proven as futile. Indeed, Lusk also writes[3] in this connection: "However clearly formulated the laws of metabolism may be, and many of them are as fixed and definite as are any laws of physics and chemistry, still the primary cause of metabolism remains a hidden secret of the living bioplasm." It is only by a broad and generous conception of all available lines of knowledge that we can ever hope to solve these great problems which, as we have already seen, involve several of the scourges of mankind.

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[1] Balfour: Edinburgh. Med. Jour., June, 1896.
[2] Graham Lusk: "The Elements of the Science of Nutrition," p. 257, 1906.
[3] Graham Lusk: *Ibid.*, p. 297.

In the present chapter I propose to show, not only that the internal secretions, as I interpret their functions, play a dominant rôle in the pathogenesis of gout, but also in two other painful disorders closely allied to this disease, migraine and neuritis, including neuralgia.

GOUT AND GOUTY DIATHESIS.

Synonyms.—As to Gout: *Podagra.* As to the Gouty Diathesis: *the Gouty Habit; Uricæmia; Lithæmia.*

Definition.—The *"gouty diathesis"* is a chronic disorder of metabolism, due to inability of the adrenal system to insure, through its active agent, the auto-antitoxin (leucocytic and plasmatic), the conversion of food nuclein into harmless, eliminable end-products. This inability may be actual, *i.e.*, due to hypoactivity of either of the organs of the adrenal system; or passive, these organs, though normal, being unable to provoke the formation of sufficient auto-antitoxin to insure catabolism of the excess of wastes with which the lymph and blood are burdened when overeating is indulged in. In either case the blood contains more or less toxic wastes of the purin type, which incite the various disorders usually ascribed to the gouty diathesis.*

Acute gout is the indirect result of an exacerbation of chronic interstitial nephritis due, in turn, to the presence in the blood of wastes which aggravate this renal disease. The free excretion of the sodium salt of uric acid, sodium biurate, being prevented, its crystals accumulate in great part in the joints, owing to the absence in their synovia, under normal conditions, of auto-antitoxin and phagocytes. The acute attack is incited by a local inflammatory process which entails the presence of these defensive agents and the conversion of sodium biurate into simpler products, especially urea, to facilitate their excretion. If this process is imperfectly carried out, the sodium biurate accumulates about the joints, forming tophi.*

Symptoms and Pathology.—An attack of acute gout is generally preceded by *premonitory symptoms, i.e.*, disorders of digestion, anorexia, flatulence, foulness of the tongue, vertigo, irritability—or the converse, mental torpor and drowsiness—palpitations with a tense, hard and sometimes irregular pulse,

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**Author's definition.*

obstinate constipation, irritative cough, tinnitus aurium, muscular cramps, neuralgia, perversions of sensation, especially at the extremities, chilliness, etc. Any of these symptoms may occur in groups which may be said to vary with each case, each sufferer having, so to say, his own set of precursory signs. These usually cease, however, immediately before the onset of the acute attack; in fact, the patient may feel unusually well.

These phenomena do not always culminate in an attack of gout; they are the expression of a condition which has been termed *lithæmia, uratæmia, uricacidæmia, uricæmia*, etc., which may appear as readily in subjects who have never suffered from acute gout, as in those who have. In the former, however, the symptoms are less marked: the tense, hard pulse is replaced by a slow pulse, and irritability with depression of spirits, gastric disorders with marked acidity and nausea, constipation, vertigo and throbbing headache, constitute the symptom-complex in the average case. Eczema and other cutaneous disorders, hay-fever, migraine, asthma, pharyngitis, and many other disorders have been ascribed to lithæmia.

The onset of the *acute attack* usually occurs at night, the patient being awakened by a very intense pain in the metatarsophalangeal joint of the great toe. Other articulations, those of the great toe of the other foot, the fingers, knees, elbows, etc., may then become involved in the morbid process. Any of these joints may be the seat of the initial attack, especially if previously injured. The affected joint becomes the seat of great tension and throbbing, and the excruciating pain is still further intensified by the slightest touch or motion. After a few hours, *i.e.*, towards dawn, relief is experienced, and the patient, after perspiring freely, is able to sleep. Some pain is experienced during the succeeding day, when the affected joint is found swollen, shining, tense and very tender. The acute pain only recurs the following night and thereafter each succeeding night, with daily remissions, until the attack passes off.

During the acute attack, the temperature is somewhat raised, *i.e.*, 100° to 102° F. (37.8° to 38.9° C.) and the pulse likewise from 80 to 100. In the affected joint, however, the opposite is the case, the temperature being considerably lower than that of the body at large, sometimes as much as 6° F.

(38° C.). Though thirst is usually marked, anorexia and even aversion for solid foods are often correspondingly great. There is nausea, rarely accompanied by vomiting, and, as a rule, constipation. The urine presents almost typical changes: it is scanty, acid and highly colored, its specific gravity being high. Uric acid and urates are precipitated on standing. The urine of subjects suffering from "lithæmia" or "uricacidæmia"—the so-called gouty diathesis—presents precisely the same characteristics. Albumin and sugar are also present during acute attacks of gout.

As the attack progresses, the affected joint or joints become somewhat œdematous—a symptom especially noticeable when large joints are involved. About the fourth or fifth day, all the acute symptoms begin to recede; the inflamed joint gradually becomes less painful, and desquamation occurs, the pain being replaced by tenderness, itching—sometimes quite severe—and stiffness.

Such an attack usually lasts from six to ten days, but remission may appear and greatly prolong it. This is apt to occur in cases of long standing. When complete recovery is reached, the patient may be in better health than before the attack.

Recurrence of a seizure may at first take place only after a year, but the intervals usually become shorter as time progresses until the attacks recur repeatedly in a twelve-month. As they become more frequent, the pain loses its severity, but the patient steadily becomes weaker, the joints do not as readily resume their freedom of action, and may remain, in fact, swollen and sensitive, the case lapsing into one of chronic gout.

In asthenic cases of long duration metastasis sometimes occurs, the so-called *metastatic* or *retrocedent gout,* the symptoms, including the pain, in a joint suddenly disappearing, to reappear abruptly in some internal organ, the heart, brain, stomach, testicles, bladder or parotid gland. When the heart receives the brunt of the attack, its action becomes irregular and there is severe præcordial pain and dyspnœa. The most prominent cerebral manifestations are violent excitement with severe headache, or, conversely, hebetude; these may be associated with the gastric metastatic symptoms, namely, vomiting and diarrhœa, with severe gastro-intestinal pain and marked weakness. In the other organs named the phenomena are those of acute inflammation, *viz.*, cystitis, orchitis and parotitis. Metastatic gout of the heart and brain has been attended by sudden death.

Chronic gout generally occurs, as already stated, in cases weakened by repeated attacks, particularly in those of long standing, and in aged subjects. The affected joints then fail to undergo resolution and remain stiff and swollen. Tophi or hard masses of urates then form over them, causing them to become nodulated and greatly deformed. So great are these accumulations in some instances that dislocation of the joint is caused. The skin may also be stretched to such a degree that it sometimes breaks, allowing the chalky masses to fall out or to remain exposed. When the large joints are the seat of these accumulations, they become rigid, and the patient is gradually transformed into a cripple. Especially is this the case when the softer structures, the periosteum, tendons, bursæ, etc., are invaded by the morbid process. Almost any portion of the body, in fact, may become the seat of deposits, the eyelids, the cornea, the crystalline lens, the cartilages of the ear, nose, the skin, etc.

Pathogenesis.—The cause of the symptoms attributed to a "gouty diathesis" and of those witnessed in acute gout, is inadequate catabolism of certain food-products. As the efficiency of all catabolic (*i.e.*, digestive) processes in the body is dependent upon the adrenal system, it is primarily to the inability of this system to provoke the formation of enough adrenoxidase, nuclein and trypsin—auto-antitoxin—that the morbid process is due.[*]

The inadequacy of the adrenal system is only *relative*, *i.e.*, is not due to actual functional debility of the adrenal center and other organs of the adrenal system, in most cases of "lithæmia" or gout caused by excessive indulgence in animal food and wines containing considerable alcohol, etc.[*] Even the excessive stimulation to which the adrenal center is submitted in such cases, as shown by the resulting arterial tension, the peripheral hyperæmia, the congested face, etc., is inadequate to free the blood of toxic wastes by breaking them down to simpler and benign end-products.[*]

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[*] *Author's conclusion.*

In the majority of cases, however: those in which hereditary predisposition is present, those due to insufficient food and squalor ("poor man's gout") or to overwork, physical or mental, or to chronic lead-poisoning, both "lithæmia" and gout, acute or chronic, are the result of *actual* functional weakness of the adrenal system, and to the imperfect catabolism of waste-products which this entails.

This relegates the primary cause of gout to a nerve-center, that of the adrenals, which governs all nutritional processes. Cullen, over thirty years ago, attributed to the nervous system the primary rôle in the pathogenesis of gout. Leven, of Paris,[4] Mortimer Granville,[5] Sir Dyce Duckworth and others have strongly urged the same view, *i.e.*, that the accumulation of the pathogenic elements was the result of a neurosis. Vindevogel, of Brussels,[6] more clearly defined the nature of the central disorders, *i.e.*, "an *enfeeblement* or lessened activity of the *trophic* nervous centers, and a loss of equilibrium between the processes of assimilation and disassimilation, by which the products of disintegration are rendered incomplete or toxic to the economy."

The pathogenic influence of debility of the adrenal center may be illustrated by the connection between lead and gout, urged by Garrod (1859), Dickinson, Lancereaux, Rosenstein, Leyden and others. Nobécourt,[7] in a comprehensive study of the subject, found that it followed slow intoxication, that it appeared at about the same age as ordinary gout, *i.e.*, during the fourth decade, and that the gouty diathesis evoked by lead could be transmitted by heredity. Now, Lemoine and Joire[8] had previously ascertained that the metal *interfered with catabolism*, thus favoring the formation of uric acid and urates. Lüthje[9] found the blood loaded with uric acid in saturnine gout—a fact which available knowledge could not explain. It is clearly accounted for, however, by the fact that lead markedly depresses the functional activity of the adrenal center, and, therefore, the production of adrenoxidase. The paralytic phenomena, the wrist-drop, the wasting, etc., also show that it reduces nutrition, *i.e.*, that its action is a debilitating one. Bouchard has pointed out that gout is a result of "slowed" nutrition, *i.e.*, of inhibited metabolism. "Poor man's gout" likewise exemplifies the influence of impaired nutrition in the pathogenesis of the disease.

The gastro-intestinal disorders observed in uricæmic or gouty subjects are the normal outcome of the imperfect gastric juice and auto-antitoxin produced, since the gastric glands, as well as the pancreas, are themselves inadequately nourished when the supply of adrenoxidase in the blood is subnormal.* This applies likewise to the muscular coats of the stomach and intestines; hence the gastric dilation and constipation, the postprandial discomfort, the nausea, the acidity, the flatulence, etc., observed in such cases.* These are not manifestations of gout: they are the expression of the debilitated condition of the governing center of nutritional processes, *i.e.,* the adrenal center.*

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* *Author's conclusion.*

[4] Leven: Med. Record, May 26, 1882.

[5] Mortimer Granville: Med. Press and Circular, Feb. 15-22, Mar. 1, 1882.

[6] Vindevogel: "Nature, Causes, and Conditions of Gout," Brussels, [illegible].

[7] Nobécourt: Semaine méd., Apr. 22, 1897.

[8] Lemoine and Joire: Gazette médicale de Paris, 8 série, T. 1, pp. 1, 13, 25, 1892.

[9] Lüthje: Zeit. f. klin. Med., Bd. xxix, S. 266, 1896.

The gastro-intestinal digestive functions being imperfect, the products of digestion are correspondingly unfitted for absorption. As it is this material which the digestive leucocytes take up in the intestinal canal for conversion into nucleoproteid granules, *i.e.,* into living tissue-chromatin, they become laden not only with what products of digestion are suitable for assimilation, but also with products that have been imperfectly digested.* The leucocytes thus garner in the alimentary canal materials which are foreign to their own intrinsic functions and which ultimately become the pathogenic elements of gout.*

That broken-down leucocytes can be the source of the pathogenic elements of gout was suggested by Horbaczewski,[10] who held, however, that there was a constant proportion between the number of white corpuscles and the amount of uric acid excreted. The latter conclusion was refuted by Kolisch[11] and others, and is likewise defective from my standpoint, since we are dealing with a physiological—and therefore momentary—leucocytosis which invariably attends digestion, and not with the leucocytosis that occurs during disease, though Chalmers Watson[12] found myelocytes in the blood in the interval and during an acute attack. The fact remains, however, that leucocytes are now the recognized source of the pathogenic elements of acute gout, especially since the investigations of Burian and Schur[13] and Marès[14]. The latter observer found, moreover, that an increase of uric acid excretion occurred immediately after meals. This coincides with clinical observation. A. Robin,[15] for instance, considers "the leucocytic origin of uric acid as definitely settled" and says, referring to great meat-eaters: "The blood contains an enormous quantity of leucocytes. This is what is termed digestive leucocytosis."

On reaching the tissues, or rather the pericellular lymph-spaces, the leucocytes deal out their nucleo-proteid granules, and these are absorbed normally by the tissue-cells, and converted into living substance, *i.e.,* chromatin.* In addition to these physiologically normal elements, however, the leucocytes simultaneously secrete products of disintegration formed in these cells out of the imperfectly digested food-stuffs absorbed by them in the alimentary canal.[*] Their two products differ totally, therefore, in that the granules are useful bodies built up by the leucocyte, while the abnormal substances are products of disintegration ejected by the cell as unfit for the elaboration of living substance.[*]

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* *Author's conclusion.*

[10] Horbaczewski: Sitz. d. Wiener Acad. d. Wissen., Bd. c, Abth. iii, S. 12, 1891.

[11] Kolisch: "Ueber Wesen u. Behandlung der uratischen Diathese," Stuttgart, 1895.

[12] Chalmers Watson: Brit. Med. Jour., Jan. 6, 1900.

[13] Burian and Schur: Archiv f. d. ges. Physiol., Bd. lxxx, S. 241, 1900; Bd. lxxxvii, S. 239, 1901.

[14] Marès: Monats. f. Chemie, Bd. xiii, S. 101, 1892.

[15] A. Robin: Rev. de thérap. méd.-chir., vol. lxix, p. 37, 1902.

The identity of these wastes depends upon the stage of disintegration they have reached when excreted by the cell, and this, in turn, depends upon the digestive activity of the intraleucocytic ferment: (1) When the adrenal system is debilitated and the production of adrenoxidase is deficient, the cell is itself poorly supplied with this substance and the heat-energy liberated through its reaction with the cellular nuclein is inadequate to raise the proteolytic activity of the cytase, *i.e.*, the cell's own proteolytic ferment, to its full potency.[*] As a result, imperfect disintegration occurs, and the materials ejected by the leucocyte[*] are intermediate waste-products, *i.e.*, alloxuric or purin compounds: xanthin, hypoxanthin, purin, adenin, etc.,—all derived from nucleins (and not from proteids). Several of these bodies, especially xanthin and hypoxanthin, are poisonous; they are not only the pathogenic elements of the so-called "gouty diathesis," "uricæmia," "lithæmia," etc., but they also play an important rôle in the pathogenesis of migraine and other disorders. (2) When, conversely, the adrenal system is adequate and an ample supply of adrenoxidase is available,[*] the proteolytic process is carried on further, and instead of the toxic intermediate wastes just referred to, the leucocytes excrete a substance which, though not poisonous in itself, may, under certain conditions, provoke acute gout, namely, uric acid.

The fact that, as I pointed out in the fifteenth chapter, leucocytes ingest food-products to convert them into tissue elements, harmonises various discordant views. Horbaczewski believed that nucleins were not the direct source of uric acid; he concluded, however, that they provoked leucocytosis, and that these leucocytes, when broken up, were the source of the uric acid. Since the latter has been known to originate directly from nucleins, this interpretation has been generally discarded. Still, the prevailing view, as stated by Hammarsten, is that "the uric acid, in so far as it is produced from nuclein bases, is in part derived from the nucleins of the destroyed cells of the body [tissue cells] and in part from the nucleins or free bases introduced with the food." If, however, as I have pointed out, it is the function of the leucocytes to *ingest* all food-products, uric acid is, as was suggested by Horbaczewski, derived from these cells (mainly secreted by them with their granules in the lymph-spaces, according to my interpretation), though derived from nucleins, in accord with his opponents. Even his belief that leucocytosis played a part in the process is warranted, provided we consider it a digestion leucocytosis. Horbaczewski can be said to have been radically wrong only in believing that uric acid was not derived directly from nucleins.

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[*] *Author's conclusion.*

Another important feature of the problem is the identity of the process through which the nucleins are converted into xanthin, uric acid and other purin compounds. Contrary to the prevailing belief that "oxidation" is the direct agent, I attribute this rôle, in keeping with the views advanced in the fifteenth chapter, to a trypsin-like enzyme whose nucleolytic activity is sustained by heat-energy liberated by the interaction of adrenoxidase and nuclein secreted by leucocytes. This view harmonizes with modern experimental evidence in the present connection as it did when studied in its relations to the digestive process in the alimentary canal, the leucocytes and the tissue cells, as may be shown by a few salient facts.

The process of uric acid formation described by Kossel and Fischer was reviewed in the first volume.[16] Briefly, they showed that the alloxuric or purin compounds, including xanthin, hypoxanthin, etc., and uric acid, were disintegration-products of the nucleins, nucleo-proteids or nucleic acid of many articles of food. Horbaczewski then found that the purin compounds could be converted into uric acid, and, moreover, that when spleen pulp, which is rich in nuclein, was fed to man or animals, the output of uric acid was increased. Krüger and Schmid[17] then found that when xanthin, hypoxanthin, guanin or adenin was administered to men, the output of uric acid was likewise augmented. These facts clearly point to food-nucleins as the source of uric acid and to the latter as an advanced disintegration-product.

That a digestive ferment is the active factor in the process is sustained by recent research. Mendel,[18] for example, says in a recent (1906) paper: "Enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities of cells in almost every feature of metabolism"—a fact fully in accord with the functions I have ascribed to the "digestive triad." On page 139 of the first volume I wrote: "Horbaczewski, in a series of experiments, observed that splenic pulp, allowed to digest several hours with blood at the body temperature, gave rise to a marked increase of uric acid and nuclein bases, but that the relative amounts of these products depended entirely upon the degree of oxidation." In other words, simple digestion—and therefore a limited supply of oxygen—gave xanthin and hypoxanthin; the addition of oxygen, on the other hand, caused the formation of uric acid. Now, the constituents of the triad were obviously present: the phosphorus-laden nuclein in the splenic pulp; the adrenoxidase, rendered very active by an artificial supply of oxygen, in the red corpuscles and plasma; and the trypsin in the leucocytes and plasma.

It now becomes a question whether the tissues contain a ferment capable of converting purin bases into uric acid. Such was found to be the case recently by Schittenheim.[19] Alcohol inhibited the action of this ferment—precisely as it does, we have seen, that of adrenoxidase. More to the point, however, was the observation of Burian,[20] that muscles, and particularly the liver and spleen, contain an *oxidase* which can convert *hypoxanthin* into uric acid. This process also requires a free supply of oxygen. That, in view of these experimental facts, a deficient supply of adrenoxidase should entail an accumulation of these toxic wastes in the body is self-evident.

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[16] *Cf.* vol. i, p. 137 *et seq.*

[17] Krüger and Schmid: Zeit. f. physiol. Chemie, Bd. xxxiv, S. 549, 1902.

[18] Mendel: Jour. Amer. Med. Assoc., Mar. 24, 1906.

[19] Schittenheim: Zeit. f. physiol. Chemie, Bd. xlii, S. 251, 1904.

[20] Burian: *Ibid.*, Bd. xliii, S. 494, 497, 532, 1905.

Uric acid, though itself harmless, becomes pathogenic when, owing to imperfect elimination, from any cause, it is allowed to accumulate in the body. It may then give rise to acute gout.

An important pathogenic factor in this connection is granular atrophy of the kidneys, a condition in which the permeability of these organs is more or less reduced. It occurs in individuals who have suffered during a prolonged period from the so-called "uric acid diathesis," *i.e.,* individuals in whom, owing to insufficiency of the adrenal system, the blood is more or less laden with purin compounds.* These bodies, xanthin, paraxanthin, adenin, guanin, etc., are not only toxic, but they irritate sufficiently the renal epithelial elements, while being eliminated, to provoke after a given time the local organic lesions which interfere with the free excretion of uric acid.

A temporary accumulation of these poisons in the blood during an exacerbation of lithæmia may also cause a sufficiently marked renal congestion to interfere with the free elimination of uric acid and thus provoke an access of gout.

As is well known, considerable uric acid is found in the blood in leukæmia; and yet these cases do not suffer from gout. In these cases the kidneys are permeable. Conversely, Levison,[31] who first drew attention to the pathological importance of renal lesions in gout, writes: "In all described cases of gout in which the *post-mortem* examination is mentioned, the kidneys have been found diseased, and in almost all cases they were suffering from granular atrophy." Luff, moreover, found uratic deposits in 41 cases out of 77 cases of granular kidney. Levison also states that in all such cases, "the power of elimination of the kidneys as regards uric acid, as well as various other substances, is diminished," and that "the consequence of this defective elimination of uric acid is its retention in the blood (von Jaksch)." Since these lines were written cases of gout and lithæmia have been reported in which no renal lesions were found after death, but if we take into account the well-known fact that the kidneys readily become congested under chemical irritation, it is evident that their permeability may readily be composed during life, though no lesions be discernible *post-mortem*.

That purin compounds, xanthin, hypoxanthin, adenin and guanin, are the renal irritants, while uric acid *per se* is not, was first shown by Gaucher, in 1884. This was fully confirmed by Kolisch,[32] whose conclusion was based on observations which included experiments by Tandler. The renal lesions thus produced artificially were found by Paltauf and Albrecht to be identical with those found in gout. Croftan[33] also found that both xanthin and hypoxanthin, when injected hypodermically in the strength of 0.3 to 0.7 per cent. watery solution, for a period of several months, produced granular degeneration of the epithelial cells lining the convoluted tubules and a proliferation of the endothelium of the intertubular capillaries.

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* *Author's conclusion.*

[31] Levison: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. iii, p. 350, 1899.

[32] Kolisch: Med. Press and Circular, Dec. 18, 1895.

[33] Croftan: Jour. Amer. Med. Assoc., July 8, 1899.

If renal lesions—or inflammatory impermeability—are necessary to provoke gout, lead-gout should likewise be attended with such lesions. Levison, referring to the experiments of Charcot, Binet, Coen and d'Ajutolo, and to clinical observations "in persons exposed to lead-poisoning," says that "one of the earliest and most constant symptoms of this disease is a pathological change of the renal tubuli conducive in rather a short time to granular atrophy of the kidneys." Moreover, Garrod,[illegible] and others since, found uric acid in the blood of cases of chronic lead-poisoning. As lead depresses the functional activity of the adrenal center, and inhibits, therefore, the formation of adrenoxidase, the cause of the renal lesions is the same as in gout, *i.e.*, inadequate cleavage of ingested nucleins and the production of xanthin, hypoxanthin, etc. Again does it become evident, therefore, that gout is primarily due to any toxic capable of causing adrenal insufficiency.

In the *"gouty diathesis"* or *"lithæmia"* some of the symptoms are due to the primary depression of the adrenal system, namely, the gastro-intestinal disorders, as already stated, the vertigo, the depression of spirits and the slow pulse—all manifestations of inadequate oxygenation.* Other symptoms, however, are the result of the imperfect catabolism which this inadequate oxygenation entails, the pathogenic agents thus formed being poisonous intermediate wastes of undetermined nature, but which include xanthin, paraxanthin and other purin bases. They do not include uric acid, however, since this substance is the normal end-product of nuclein catabolism, which is as harmless in itself and as readily eliminated by the kidneys as is the normal end-product of proteid catabolism, urea. Among the symptoms produced by these toxic subcatabolic wastes are those due to the penetration of the poisons into the axis-cylinders, cell-bodies, dendrites, and other nervous elements, along with the adrenoxidase circulating through them.* Hence the migrainous headache, the neuralgia, the shooting pains, or the opposite states: anæsthesia and other paræsthesias, and also the extreme nervous irritability so frequently observed in these cases.

The symptoms of the so-called *"irregular"* or *"atypical gout"* observed in lithæmic subjects, and which sometimes alternate with attacks of true gout, are due to the same subcatabolic poisons, including also xanthin and other purin compounds, but not to uric acid. In addition to the lithæmic symptoms just enumerated, these poisons give rise to eruptions and pruritus (as excretion products), flushes of heat, sometimes limited to the palms and soles, muscular pains, especially in the back, and inflammatory phenomena in various organs, *i.e.*, the bronchi, pericardium, bladder, gums, etc., and also in the vascular walls, leading to arteriosclerosis. Many other disorders, migraine, epilepsy, tetanus, eclampsia, etc., in which these subcatabolic poisons play the leading rôle are reviewed in this chapter.

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* *Author's conclusion.*

[illegible] Garrod: Med. Chir. Trans., vol. xxxi, p. 83, 1848.

In both of the above syndromes—which in reality differ only in name—certain of the phenomena are due to a direct action of the subcatabolic poisons upon the centers in the pituitary.* The flushes of heat and a febrile process in which the temperature is raised two or three degrees F. are often concomitant general phenomena which point to excitation of both the adrenal center and the sympathetic center, and to increase of the propulsive activity of all arterioles.* Fever denotes here an effort to raise the nucleolytic activity of the blood, *i.e.*, its asset in auto-antitoxin, and thus to convert the subcatabolic poisons into uric acid, *i.e.*, into a benign eliminable end-product.*

Uric acid is found in the urine of man and other carnivorous mammalia, and abundantly in that of birds. In the latter and in the scaly amphibians, in fact, "the greater part of the nitrogen of the urine," as stated by Hammarsten, "occurs in this form." It is evident that in these animals it occurs as a terminal waste-product, that as such it is itself non-toxic, and, finally, that it is eliminated physiologically, that is to say, without injuring the kidneys or any other organ. That uric acid is non-toxic even in large doses was shown experimentally by Bouchard.[25] This was fully confirmed by Croftan,[26] both as to large quantities, and as to small quantities given hypodermically a long time, *i.e.*, three months. Microscopical examination of the kidneys in the animals of the latter series revealed no abnormalities. Deposits of urates were found in none of the structures examined, including the synovial membranes and joints.

We have seen that xanthin, paraxanthin, etc., produced marked irritation of the kidneys; Salomon,[27] Filehne,[28] Pachkis and Pal[29] and Rachford,[30] have shown that these substances can provoke various nervous disorders, including migraine, muscular rigidity, tonic spasms, and also marked arterial tension, arteriosclerosis, dyspnœa, cyanosis and rigor mortis. Paraxanthin obtained from the urine of a case of migraine which lapsed into "epileptoid" tonic spasms, described by Rachford, reproduced the latter—"almost a tetanus"—in mice. Salomon found that 0.0005 gm. ($^1/_{130}$ gr.) sufficed to tetanize a mouse fatally.

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* *Author's conclusion.*

[25] Bouchard: "Lectures on Auto-Intoxication in Disease," transl. by Oliver, p. 51, 1894.

[26] Croftan: N. Y. Med. Jour., Aug. 11, 1900.

[27] Salomon: Archiv f. Physiol., S. 426, 1882, and other papers.

[28] Filehne: DuBois-Reymond's Archiv., S. 72, 1886.

[29] Pachkis and Pal: Wien. med. Jahr., Bd. xi, S. 612.

[30] Rachford: Med. News, May 26, 1894.

Croftan,[illegible] moreover, found in all so-called uric acid disorders, "an absolute increase over the normal of the sum of uric acid and alloxuric bases" and considers the latter as the only true pathogenic agents. He also attributes their formation to deficient oxygenation, for "if oxygenation is sufficient,* says this investigator, "we have the formation of uric acid; this is the normal process." This obviously brings us back again to debility of the adrenal system as the primary cause of all so-called "uricacidæmias."

These facts indicate, moreover, that xanthin and paraxanthin are not only renal irritants, but also intense neural excitants. These phenomena are readily accounted for since I have shown that the blood-plasma, the carrier of these poisons, circulates *in* the neural elements themselves, axis-cylinders, the fibrils of the cell-bodies, the dendrites, etc.

The *premonitory symptoms* of acute gout are similar to those of "lithæmia" and "irregular" gout and are due to the same subcatabolic poisons. Here, however, the pathogenic influence of xanthin, paraxanthin, etc., assumes the primary rôle. *It is to the renal disorder evoked by these poisons that the attack of acute gout is due* when the quantity excreted is sufficient to provoke marked hyperæmia or inflammation, whether the kidneys be previously diseased or not.* Hence the facts (1) that the premonitory signs cease before the onset of acute attack, (2) that they are not always followed by an accès, or (3) that between the premonitory signs and the onset of acute gout there is usually a period of relief and well-being—all the result of a more or less complete renal elimination of the alloxuric poisons with what proportion of them may have been further catabolized into uric acid.* The attack of gout fails to develop if the kidneys are left permeable after this eliminatory process; conversely, it develops if the renal congestion produced is sufficiently active to inhibit markedly the excretion of uric acid and to cause it to be retained in the body in sufficiently large quantities.

Although renal disease is probably present in the vast majority of cases of gout, as we have seen, it cannot itself be the direct cause of the attack, since the latter would be continuous—in keeping with the renal lesion. As the average attack usually lasts but a few days and is followed by a period of health, it is evident that a temporary exacerbation of the local lesions or an ephemeral inflammatory process is necessary to account for it. Xanthin, hypoxanthin, etc., being irritants of the renal elements, become normal causes of this temporary morbid process, especially in view of the fact that even large doses of uric acid given orally or hypodermically, are harmless.

Although under these conditions, the excretion of uric acid or its salts during the attack must vary with the functional efficiency of the diseased kidneys, the nucleolytic activity of the blood, etc., and therefore, to a great extent, in different cases, and at different times in the course of a given case—as observed clinically—the fact remains that various authors have noted a sudden diminution of the uric acid excretion immediately before the acute attack. His,[illegible] for example, found that while the average quantity of uric acid excreted by lithæmic subjects was similar to that excreted by healthy persons, "an acute attack of gout was practically invariably introduced by a very marked depression in the quantity of uric acid, or even its complete disappearance. This occurred on the day before the attack in 10 instances, two days before the attack in 2 instances, and three days before the attack in 3 instances." This is explained by the course of events outlined in the general text: the uric acid accumulated in the body (owing to increasing renal inflammation) during the one to three days preceding the attack, and the latter broke out as soon as the volume of uric acid reached a sufficient level.

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* *Author's conclusion.*

[illegible] Croftan: Jour. Amer. Med. Assoc., July 8, 1899.

Although carried by the blood-stream to all parts of the organism, uric acid accumulates in fluids such as the synovia of joints, lymph, etc., and tissues such as cartilage, ligaments, tendons, bursæ, etc., because it is not as actively exposed therein to the substances which in the blood serve to antagonize its morbid effects.* Gout being in reality a febrile disease, and the expression of an autoprotective function, the blood becomes loaded with defensive materials, namely, leucocytes capable of acting not only as phagocytes, but also as the purveyors of the trypsin and nuclein which, with the adrenoxidase dealt out by the red corpuscles, constitute the auto-antitoxin.* As uric acid can be further catabolized under these conditions to still simpler products, urea, allantoin, glycocoll, and other bodies more readily excreted by the congested kidneys than uric acid, the blood, especially while in transit through the liver, is kept relatively free of uric acid as long as the febrile process lasts. Not so, however, with the joints (and nerves) and other structures enumerated. In synovia, for example, the red corpuscles and leucocytes are absent under normal conditions, and uric acid failing to be destroyed therein as elsewhere, it accumulates in the joint.* During the attack the latter is the seat of an exudation containing many leucocytes, but as compared to the blood, very few red corpuscles. As the local supply of adrenoxidase, of which these cells are the carriers, is deficient, the heat energy available to raise the catabolic efficiency of the trypsin is far below that of the blood, and the curative process is slow in proportion. Hence the fact that the temperature of an affected joint in gout is sometimes as much as 6° F. (3.3° C.) lower than that of the body at large.*

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* Author's conclusion.

[illegible] His: Deut. Archiv f. klin. Med., Bd. lxv, S. [illegible], [illegible].

In the joint affected the lesion is that of a low grade of inflammation, involving, however, a certain degree of softening of the exposed cartilage, and penetration therein of the acicular crystals of the sodium salt of uric acid, *i.e.*, sodium biurate. The curative process therein is a counterpart of that carried on in the blood. It is efficient, therefore, in proportion as the activity of the adrenal system is marked, *i.e.*, in proportion as the relative volume of adrenoxidase, nuclein and trypsin in the fluids is great.* As leucocytosis is likewise commensurate, all else being equal, with the adrenal activity, there is (1) breaking down of the uric acid salt into simpler products, especially urea, by the auto-antitoxin, and (2) phagocytosis of the detritus—the cartilage being left somewhat granular.*

As stated by Lazarus Barlow,[53] "it has been repeatedly proved by quantitative analysis that the amount of uric acid in the blood is at its maximum immediately before an attack of gout, and diminishes immediately after the attack has subsided. This, taken in conjunction with the fact that the crystalline sodium biurate is actually found in joints that have been the seat of gouty inflammation, is sufficient evidence that gout depends upon the retention of uric acid." Analysis of these statements, which are based on a comprehensive view of the literature of the subject, will indicate that my interpretation of the process—that submitted above—is in accord with experimental evidence, besides harmonizing with the conclusions submitted in the foregoing pages.

"The power of the animal organism to catabolise uric acid like other nitrogenous compounds" is considered by Mendel, "one of the fruits of modern research which has profoundly changed our attitude toward the problems of purin metabolism." Wohler and Frerichs,[54] Wiener[55] and others have shown that uric acid could be destroyed in great part in the organism, and more or less completely converted into urea. Salkowski, Mendel, Brown, Minkowski have pointed to allantoin as an important product of uric acid, Wiener to glycocoll, etc. Chassevant and Richet,[56] Ascoli[57] and others found that the liver played a very prominent part in this process. Schittenhelm[58] recently found that *two* sets of ferments were concerned in this process, one of which *hydrolyses* and detaches the ammonia group, while the other *oxidises* and breaks down the uric acid. The former is obviously the tryptic ferment and the latter adrenoxidase.*

That the joints should, conversely, be the seat of slow catabolism, is shown by the fact that even during active inflammation the local temperature is relatively low. Thus, Balfour[59] refers to "the absence of excessive heat in joints affected with gout" and to the fact that "some observers have found such joints lower in temperature than surrounding parts." Dyce Duckworth[60] observed a difference of five degrees.

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* *Author's conclusion.*

[53] Lazarus-Barlow: "Manual of Gen. Pathol.," second edition, p. 597, 1904.

[54] Wohler and Frerichs: Annal. d. Chem. u. Pharm., Bd. lxv.

[55] Wiener: "Ergebnisse der Physiologie," Bd. i, Abt. i, 1902.

[56] Chassevant and Richet: C. r. de la Soc. de biol., vol. xlix, p. 743, 1897.

[57] Ascoli: Archiv f. d. ges. Physiol., Bd. lxxii, S. 240, 1898.

[58] Schittenhelm: Zeit. f. physiol. Chemie, Bd. xlv, S. 121 u. 161, 1905.

[59] Balfour: *Loc. cit.*

[60] Dyce Duckworth: "Treatise on Gout," London, 1889.

James Tyson[41] also says that "the local temperature, notwithstanding the sensation of heat, is five or six degrees below that of the axilla at the same time."

The urine often shows clearly the presence of renal obstruction: we have seen that it is scanty, highly colored, etc. While the uric acid, excreted in twenty-four hours before and during the attack, may be markedly reduced, as emphasized by Bartel, Dyce Duckworth and others,[42] having obtained but 0.2 to 0.5 gm. (3 to 8 grains) from 100 gms. ($3^{1}/_{2}$ ounces) of urine (which in health gives 1 to 1.5 gm.), along in some cases with all excrementitious products, the end of the attack is characterized by a free excretion of urea and uric acid which continues several days. Still, the clinical evidence on this score is quite contradictory. This is readily accounted for by the fact that the catabolizing properties of the blood and the degree of renal disorder may be said to vary with each case.

When the uric acid salts or biurates accumulated in joints (and elsewhere) fail to be adequately broken down to simpler products, they accumulate *in situ*, forming tophi. At first mortar-like and soft, these nodules gradually harden, and as succeeding accumulations occur, the joints become increasingly ankylosed and distorted. The development of tophi, *i.e.*, of *chronic gout*, is due to debility of the adrenal system, *i.e.*, to insufficiency in the body-fluids of the "digestive triad," *i.e.*, of auto-antitoxin, of the sensitizing thyroidase. and of the phagocytic leucocytes whose mission is to prevent such accumulations by ridding the regions attacked of all detritus.*

We have seen that chronic gout occurs in cases weakened by repeated attacks and in aged individuals—all subjects in whom debility of the adrenal system is self-evident. As stated by Levison, "the urine in chronic gout is pale and watery" and contains "casts of renal tubuli, hyaline or granulated," evidence of marked renal implication, while "the patients are weak and pale." Indeed, as taught by Bouchard[43] over twenty years ago, the phenomena often observed in chronic gout, œdema, cardiac lesions, cerebral and gastric disorders, etc., are in reality renal, and the patient dies of his renal disease.

Treatment.—MEASURES INDICATED DURING AN ACUTE ATTACK.—Between the use of "flannel and patience" recommended by Cullen and the modern local hot-air bath at 300° F. and above, applied to the affected joint, are many devices such as the hot douche, the local sweat pack, the local vapor bath, radiant heat, the hot dry pack, etc., the application of hot alcohol, hot anodyne liniments, etc., which, when judiciously employed, prove very efficacious. The mode of action of *heat* in this connection illustrates that of remedies which, given internally, have likewise been found useful. During the attack, the affected joint, we have seen, is invaded by leucocytes which supply it with this ferment and nuclein, while red corpuscles, the purveyors of adrenoxidase, are relatively few. Though trypsin and nuclein are plentiful, therefore, in the exudate the adrenoxidase is scanty, and the heat-energy liberated when it combines with nuclein is insufficient to raise the activity of the trypsin to a level that will insure prompt conversion of the accumulated uric acid into benign and eliminable products.* As the source of the heat-energy required in the process is immaterial, hot lotions, hot dry air, etc., are effective in proportion as they are able to raise the temperature of the interior of the joint to a level at which trypsin, *i.e.*, the local auto-antitoxin, becomes very active.* Hence the relatively great efficiency of hot dry air, which brings to bear upon the surface greater heat than any other procedure. *Massage*, when it can be borne, hastens local resolution by a similar process.*

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* *Author's conclusion.*

[41] James Tyson: "Practice of Medicine," third edition, p. 785, 1903.

[42] Bartel, Duckworth and others: Cited by Pfeiffer: Lancet, Jan. 3, 1891.

[43] Bouchard: "Mal. par ralentissement de la nutrition," second edition, p. 282, 1885.

We have seen that, as stated by Hammarsten, temperature exerts "a very important influence" on ferments. Roberts[44] showed, moreover, that the activity of trypsin increased with rising temperature until 60° C. was reached. Artificial heat was used here, the trypsin being *in vitro*. Active congestion of the joint, encouraged by using it, is beneficial in much the same way. Balfour[45] refers to several cases mentioned by Cullen, Sir William Temple, Gairdner and others, who "walked off" their attacks, and to Boerhaave's advice to take much and continuous exercise, and to rub the affected part, etc. Any procedure which increases the activity of the local circulation not only augments the proportion of "digestive triad" supplied to the part, but raises also the local temperature, and hastens the removal of detritus.* Hence the recognized value of massage.

Appropriate *purgatives* at the outset of an acute attack serve several purposes: they enhance the catabolic activity of the blood not only in the liver where the breaking down of toxic wastes is most active, but also in the body at large, and thereby tend to arrest the accumulation of uric acid in the joints.* Moreover, by increasing the excretory activity of the intestinal canal they reduce the work imposed upon the kidneys and diminish the congestion of these organs.*

Most active in this connection are the *mercurial purgatives*. As they stimulate powerfully the adrenal center, the production of auto-antitoxin is increased and the specific action of these agents on the liver enhances actively the destruction of uric acid.* *Calomel* or *blue-mass* gives excellent results. *Colocynth* and *jalap* have likewise been used, but their effect upon catabolism is much less marked. A saline purgative given after either of these materially aids the beneficial effect by causing flushing of the intestine with a serous discharge.

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* *Author's conclusion.*

[44] Roberts: Proc. Royal Soc. London, vol. xxxii, p. 158, 1881.

[45] Balfour: *Loc. cit.*

The beneficial action of calomel has been emphasized by Grimm.[illegible] Having employed it expecting merely a purgative effect in a case, he obtained marked amelioration in the condition of the joints. Similar results were then observed in 18 out of 20 cases which form the basis of his report. Levison states that in England, where gout is especially common, practitioners often begin the treatment "by the administration of a free purgative: calomel and jalap or mistura sennæ composita."

The remedies which have held their own in gout, produce their main effect by acting much as do cholagogue purgatives. *Colchicum* is the most prominent of these agents. Like purgatives, it increases general catabolism in the blood, and particularly in the liver. Given in excessive doses, however, or too long, it stimulates powerfully, not only the adrenal center, but also the vasomotor and sympathetic centers, producing not only a marked increase of vascular pressure prejudicial to the kidneys, but also exposing the heart to inhibition by causing undue constriction of its coronary arteries.* The danger-signals are active purgation and weakness of the heart's action with, perhaps, some irregularity. It is to its action on the sympathetic center and the constriction of the peripheral arterioles that it owes its analgesic property, the supply of arterial blood to the sensory terminals of the skin being thus reduced.* In the average case 10 to 20 minims (0.61 to 1.22 gm.) of the wine may be given every three hours. Colchicine is preferred by many clinicians, the dose being $^1/_{50}$ grain (0.0013 gm.) every four hours, or better $^1/_{100}$ grain (0.00065 gm.) every two hours. The drug should be withdrawn when the pain is controlled (usually within 48 hours) or when purgation is marked.* The *Carlsbad waters* owe their marked beneficial effects in gout to their main constituent, a purgative salt, sodium sulphate, and to the ingestion of considerable water which their use entails; the active ingredients of Scudamore's remedy are also purgative salines, magnesium sulphate and magnesia.

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* *Author's conclusion.*

[illegible] Grimm: Deut. med. Woch., Bd. xix, S. [illegible], [illegible], [illegible].

Colchicum is generally considered as a specific for gout. H. C. Wood[47] states that "so far as our knowledge reaches, colchicum or its alkaloid, when given in therapeutic doses, produces no definite symptoms save purgation." That it does more, however, is shown by evidence quoted by this author. As I previously stated, the curative process is due to the breaking down of uric acid into simpler products, urea, for instance: Christison found "in the colchicum-urine the *proportion* of urea nearly double;" in rheumatism, Maclagan[48] also found that "the *proportion* of urea was very greatly increased." This is not controverted either by the observations of Graves and Gardner, that the urates (*total*) "diminish under the use of the medicine," since the purgation deviates the excretory current from the kidneys, or by those of Noel Paton,[49] who found that "small doses of colchicum increased very distinctly the elimination of urea and uric acid, as well as the amount of urine; while large doses lessened the amount of urinary secretion and increased slightly the daily elimination of urea and uric acid" in dogs. Although the kidneys were, of course, not diseased, the catabolic action of the drug is emphasized by the effect of small doses, while the derivative action of purgative doses is shown by that of the larger doses. In the light of my views, therefore, the experimental testimony is not discordant, as generally believed.

The physiological action of *salicylic acid* and the *salicylates* in gout differs only from that of colchicum in that these drugs do not provoke purgation. By stimulating the adrenal they enhance the blood's catabolic activity, especially in the liver, and promote thereby the elimination of urea and uric acid.* As does colchicum, they relieve pain by stimulating the sympathetic center (a process that entails the same danger of arresting the heart when used recklessly), and thus causing constriction of the peripheral arterioles.* By thus reducing the blood supplied to the cutaneous capillaries, they lower the superficial temperature (its so-called antipyretic action).*

Some clinicians prefer the salicylate of sodium to colchicum, but the great majority regard it as inferior to the latter. Ten grains (0.6 gm.) every two hours give the best results. Many other preparations of salicylic acid are now available, but all act more or less actively in the same way.

The action of the salicylates on the liver is often overlooked. Wood, however, says in this connection: "The belief of many clinicians that the salicylates have a distinct action in stimulating the biliary secretion seems to have a solid experimental foundation" and refers to the researches of Moreigne,[50] Bain, Pfaff and Balch. As to their action on metabolism, he states that the experiments have been "so numerous and concordant in their relations as to prove that in the normal man or animal, salicylic acid and its preparations increase to a very great extent the elimination of urea and uric acid."

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* *Author's conclusion.*

[47] H. C. Wood: "Therapeutics, etc.," twelfth edition, p. 535, 1905.

[48] Maclagan: Edinburgh Jour. of Med. Sci., vol. xiv, p. 3, 1852.

[49] Noel Paton: Brit. Med. Jour., July 31, 1886.

[50] Moreigne: Arch. de méd. expér. et d'anat. pathol., vol. xii, p. 209, 1900.

Haig[51] observed that sodium salicylate failed when there was general debility, and in sequence to colchicum. In the former case, the adrenal center is itself sometimes too debilitated to react under the relatively weak stimulation of the salt, though it *would* act under a more powerful excitant, potassium iodide, for instance.* That it should not act after colchicum is obvious, since the latter drug is the more powerful adrenal stimulant.*

Curative properties are ascribed to *piperazine* mainly because it forms with uric acid *in vitro* a urate which dissolves in forty-seven times its weight of water. In practice, however, though it tends to increase the excretion of urea and diminish that of uric acid, it does not produce effects indicating that in the blood-stream it behaves as it does *in vitro,* and it has been found less efficient than either colchicum or the salicylates by the majority of clinicians, in acute gout. There is ground for the belief, however, that it tends to prevent the development of acute attacks by stimulating sufficiently the adrenal center to insure the breaking down of renal irritants, xanthin and hypoxanthin, into urea.* It is administered in the form of "piperazine water," a quart of which contains 15 grains (1 gm.) of piperazine. During acute gout this quantity is given in divided doses; as a prophylactic one-half of this, *i.e.*, 1 pint (500 gms.) daily is sufficient.

The large quantity of water thus taken is unquestionably an important feature of the remedy's action. Still, Biesenthal and Schmidt[52] obtained beneficial effects with the salt itself. Schweninger[53] found it especially efficacious when given with considerable water. In the form of "piperasin water" it has been found efficacious by Wilcox,[54] Page,[55] Eshner[56] and others, in various gouty conditions, as well as by a large number of foreign observers.

The ingestion of large quantities of *pure water* during an attack and in disorders due to the gouty diathesis facilitates greatly the elimination of uric acid by the kidneys, owing to the lower specific gravity of the blood-fluids produced. This action is enhanced, however, when alkaline *mineral waters* are used instead, especially those of which sodium carbonate and sodium chloride are the main constituents. They not only increase the fluidity of the blood, but facilitate osmosis, the sodium ion activating simultaneously cellular metabolism, and, therefore, catabolism. When in acute gout the fever is at all marked, the free use of beverages of this kind is of paramount importance.

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* *Author's conclusion.*

[51] Haig: Lancet, Aug. 12, 1899.

[52] Biesenthal and Schmidt: Provincial Med. Jour., Mar. 1, 1892.

[53] Schweninger: Jour. Amer. Med. Assoc., Sept. 24, 1892.

[54] Wilcox: Med. News, Nov. 27, 1897.

[55] Page: Med. News, Oct. 13, 1900.

[56] Eshner: Phila. Med. Jour., Apr. 23, 1898.

Over fifty years ago, Guelle showed that pure water ingested in large quantities increased the elimination of uric acid, and that after this process had continued a few days, the excretion fell and sometimes ceased, the blood having been, so to say, relieved of all free uric acid. Robin[57] recently confirmed this observation and noted that in women who, to reduce flesh, avoided fluids, the urine became dense, loaded with uric acid, and that renal lithiasis followed. The rôle of the blood-salts in osmosis has been reviewed at length elsewhere. Both Jacques Loeb and Overton[58] have shown that "the Nations of the blood as well as the sea-water are essential for the maintenance of life-phenomena." The importance of the alkaline salts in all febrile processes was emphasized in a preceding chapter. In stations such as Vichy and Carlsbad, where the waters are strongly alkaline, the temporary aggravation is sometimes witnessed; this is due to the liberation of pent-up uric acid, through increased osmosis, and is rightly considered by the local physicians as a favorable sign. Sir William Roberts's belief that sodium salts are harmful in gout is not sustained by practical evidence. As stated by Burney Yeo,[59] "notwithstanding the experimental evidence to the contrary, it has been amply demonstrated that the alkaline sodium salts have an effect upon the hepatic functions and do favorably influence gouty conditions."

Prophylactic Treatment.—Having ascribed the premonitory symptoms of acute gout, the various phenomena included under the "gouty diathesis," and chronic gout, to a common cause,* the measures indicated are necessarily similar in all these supposedly different conditions, a fact sustained by clinical experience.

The prophylactic measures indicated, in the light of the pathogenesis described in the foregoing pages, are (1) to reduce the intake of nucleins and thereby the purin bases of which they are the source, and (2) to enhance the functional efficiency of the adrenal system in order to insure the adequate conversion of toxic intermediate wastes into nontoxic and eliminable end-products.*

Reduction of the Intake of Nucleins.—The toxic intermediate waste-products being all nuclein derivatives, the pathogenic activity of food-stuffs is commensurate with the quantity of nuclein they contain. Especially rich in this connection are glandular organs, such as liver, thymus (sweetbread) and kidney. This applies likewise to brain tissue, an enormous aggregate of nerve-cells, the cell-bodies of which all contain nuclei. Muscle tissue, *i.e.*, meat, is less rich in this particular, but hypoxanthin and xanthin are the main purin product of its nuclein. Beef extracts and the gelatinous extracts of tendons, bones, etc., are likewise rich in nucleo-albumins which yield the same purins—those, we have seen, that irritate the renal elements, and which take part in the pathogenesis of the various disorders of the "gouty diathesis."

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* *Author's conclusion.*

[57] Robin: *Loc. cit.*

[58] Jacques Loeb and Overton: "Studies in General Physiology." Pt. II, p. [illegible], 1905.

[59] Burney Yeo: Therap. Gazette, July 15, 1901.

The glandular tissues, sweetbread, liver, etc., should be strictly avoided. As to meats, the indications vary with the case; in excessive eaters, especially those subject to cutaneous disorders and in patients who suffer from migrainous attacks, flushes, etc., a temporary—a year or two at most—omission of heavy meats, *i.e.*, beef, mutton, pork and veal, from the diet, and the concurrent ingestion of at least a quart of pure water daily, is often very efficacious. In debilitated subjects, on the other hand, in which no evidence of renal lesion is present, lean beef may be allowed, but simultaneously with remedies that stimulate the adrenal center.*

Milk, fish, poultry and eggs, vegetables, fruit, especially strawberries, oranges and apples, butter, light bread and biscuits, with tea, coffee or cocoa in moderation, etc., are all permissible. Alcoholic beverages, malt liquors, sweet and heavy wines, are never beneficial and are not craved for when water is taken in large quantities. As alcohol becomes oxidized in the blood it antagonizes catabolism, and thus tends to aggravate the morbid process.* Meals should be taken at regular intervals.

* In view of the experiments of Gaucher, confirmed by Kolisch, Tandler and Croftan, as to the pernicious influence of xanthin and hypoxanthin upon the kidneys, Halliburton's statement[illegible] that meat diet causes an increase of uric acid "mainly because it increases the exogenous uric acid from the purin bases, especially the hypoxanthin which it contains" is suggestive, since it is obvious that inadequate catabolism must increase the proportion of the latter and tend to promote not only renal lesions, but also general "gouty" disorders. Kionka and Frey[illegible] recently confirmed the observation of Kochmann, that excessive meat-feeding caused organic lesions in the liver and kidneys, and also those of Walker Hall, in rabbits, in which similar lesions

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* *Author's conclusion.*

[illegible] Halliburton: "Physiol. Chem. of Muscle and Nerve," p. 45, 1904.

[illegible] Kionka and Frey: Zeit. f. exper. Pathol., Bd. ii, S. 1, 1905.

were produced by injections of hypoxanthin. Robin[62] found experimentally, that in man the addition of collagenous parts of meat, bones, ligaments, etc., to the diet, increased markedly the production of uric acid—which would mean that of hypoxanthin and xanthin in debilitated subjects. For the influence of alcohol the reader is referred to the article on this agent.

Measures to Increase the Functional Activity of the Adrenal System.—Those of our remedies which approach nearest the normal physiological stimulant of the adrenal thyroidin, in its effects, namely, *iodine* and its salts, especially the potassium and sodium iodide, are of recognized value in this connection, when employed in gradually increased doses, beginning with 5 grains (0.3 gm.) three times daily in a tumblerful of water. *Thyroid extract* is also efficacious, but not in the large doses usually recommended, which increase too suddenly general metabolism and increase the waste-products in proportion; 3 grains (0.2 gm.) after meals may be given without increasing the dose.[*] *Oxygen* inhalations begun the third day after beginning the use of the thyroid extract will hasten the curative process, since at that time the blood will be found by the coagulation test to contain a larger proportion of fibrin ferment, *i.e.*, adrenoxidase.[*] (See also p. 782, vol. i.)

Among other agents that have been found efficacious are *strychnine* and *nux vomica,* which not only stimulate the adrenal center, but also the vasomotor center, thus causing constriction of the mesenteric trunks and projection of the blood towards the peripheral capillaries, including those of the liver[*] where poisons are most actively destroyed. Strychnine is only of real use, however, in debilitated cases, attended with pallor.[*] This applies likewise to iron, to promote the formation of hemoglobin.

The value of the iodides in gout is well known. Bain[63] found potassium iodide of "peculiar value" in chronic gout, and that it retarded the development of vascular and renal changes. Haig employs the sodium iodide with success, using in conjunction, sometimes, ammonium chloride. I have found thyroid extract, when used as recommended above, of considerable value in gouty cases in which migraine was a prominent symptom. Inhalations of oxygen gas were employed by Croftan[64] with "striking" results, "both as regards amelioration of the subjective symptoms" as well as laboratory findings. That this measure should prove of still greater value when the blood's adrenal secretion is increased by means of thyroid extract, seems obvious. Strychnine has been recommended by Robin[65] and others.

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[*] *Author's conclusion.*

[62] Robin: *Loc. cit.*

[63] Bain: Brit. Med. Jour., June 9, 1900.

[64] Croftan: N. Y. Med. Jour., Aug. 11, 1900.

[65] Robin: Bull. gén. de thérap., vol. cxlvii, p. [illegible], 1904.

MIGRAINE.

SYNONYMS.—*Sick Headache; Megrim; Hemicrania; Bilious Headache.*

Definition.—Migraine is due to marked hyperæmia of the nerves and nervi nervorum of the painful area, the result, in turn, of abnormal constriction of all arterioles, excepting those of that area which fail to contract owing to functional weakness (sometimes due to organic disease) of their walls. The general constriction of the arterioles is due to excitation of the sympathetic center by toxic wastes, probably of the purin group, which accumulate in the blood owing to hypoactivity of the adrenal system, the insufficiency of auto-antitoxin reducing correspondingly the catabolic properties of the blood.**

Symptoms and Pathology.—Migraine corresponds with epilepsy in its pathogenesis and symptomatology, and the latter may, therefore, be divided into three stages: (1) a prodromal stage or aura, (2) a stage in which the sympathetic system is morbidly active, and (3) a stage in which the vasomotor overactivity is superadded.*

The *prodromal* stage or *aura* differs from that of the epileptic aura, in that it is relatively prolonged, lasting minutes, hours, or days even, in some cases. It may include one or more of the following phenomena: a sensation of pressure at the seat of oncoming pain, dark or bright spots, flashes and other luminous sensations, impaired vision, tinnitus, olfactory and other sensory auræ, vertigo, confusion of ideas, hallucinations, visions, hebetude, somnolence and despondency, anæsthetic areas in the scalp and face, aphonia, etc. In rare instances the premonitory signs occur during sleep, in the form of exciting dreams, violent nightmares, etc. Anorexia, nausea and creeping chills are common precursors of the migrainous attack, however, which usually begins in the morning.

In the *sympathetic* variety, the ordinary migraine, the patient is pale, the features are contracted and the surface is relatively cool, the temporal arteries being small and tense. The pain, at first dull, then more or less acute, is usually unilateral and often located in the supra-orbital, frontal and temporal regions; sometimes, however, it extends to the parietal and even the occipital regions. In some cases, the disorder is quite localized, the site of pain being hypersensitive, while the surrounding tissues are relatively cool and insensitive. Unilateral salivation, lachrymation and diaphoresis are occasionally observed. In rare instances, the pain leaves one region to appear in another, which may be quite remote, the stomach, for instance, then suddenly returns to its former location.

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* Author's conclusion.
**Author's definition.

Vomiting may occur early in the course of the seizure, but usually it heralds recovery. At the end of a few hours, sometimes days, the patient falls asleep and is soon about. Such attacks occur with more or less regularity, perhaps once a month, every other week, etc., year after year. In men they often cease after middle life, and in women after the menopause.

This form of migraine is primarily due to irritation of the sympathetic center.*

This form, Dubois-Raymond's angiospastic hemicrania, is now generally attributed to a disorder of the sympathetic system. Mollendorff and Latham[illegible] both attributed migraine to morbid activity of this system, but "in consequence of a defective control or inhibition by an exhausted or enfeebled cerebro-spinal system." The kinship with epilepsy is now generally recognized. Rachford,[illegible] for instance, says, in a comprehensive study of this relationship: "All writers on this subject are agreed that migraine and epilepsy are kindred diseases, and that this kinship is so close that these diseases are not infrequently twin inheritances from the same neurotic ancestors," and refers to Tisset, Parry, Liveing and Gray as having emphasized this kinship, by cases in which epilepsy appears, and the epilepsy returning when the migraine disappears." Spiller[illegible] likewise lays stress on this kinship. In a case reported by H. C. Wood[illegible] the paroxysms began as a migraine, including the prodromes; this lasted two or three hours, then lapsed into a typical epileptic fit, the patient frothing at the mouth, biting his tongue, etc.

The pain, in this form of migraine, is due to marked congestion in the area involved, the result, in turn, of a passive, strictly localized, dilation of the arterioles of that area.* While all the other arterioles of the body contract under the impulses received through their sympathetic terminals, the arterioles of the region affected fail to do so, owing to lesions of their muscular layer.* The nerve region being rendered intensely hyperæmic—since the blocking of all other arteries tends greatly to increase the local blood-pressure—severe pain, due mainly to pressure and hyperæmia of the local nervi nervorum, is caused.[*]

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* *Author's conclusion.*

[illegible] Mollendorff and Latham: Cited by Liveing: "On Megrim, Sick-headache, etc.," p. 319, 1873.

[illegible] Rachford: Amer. Jour. Med. Sci., Apr., 1896.

[illegible] Spiller: *Ibid.*, Jan., 1909.

[illegible] H. C. Wood: Med. News, Dec. 29, 1894.

The general sympathetic constriction of the systemic arterioles is shown by the marked relaxation of the abdominal viscera, *i.e.*, the stomach, intestines, liver, etc., to which French clinicians, Glénard, Trastour, Dujardin-Beaumetz and others, have called attention. Their observations were fully confirmed by the more recent researches of Mangelsdorf,[70] in 409 cases, all of which, with one exception, had marked gastric dilation. Examination of a large number of cases suffering from nervous disorders failed to show this symptom, with the sole exception of epileptic subjects. Constriction of the gastric arterioles readily accounts for this phenomenon; the blood supplied to the muscular walls being inadequate, they relax.[*] This applies as well to any organ, since the irritability of the sympathetic is of central origin, and, therefore, general—in opposition to Dubois-Raymond's view, that it is limited to the cervical sympathetic. The many cases in which tingling and other forms of paræsthesia occur in various parts of the body also point to a central origin.

As to the localized vasodilation which gives rise to pressure upon the nervi nervorum, Mollendorff, Latham, Guttmann, Wilks and Ellenburg have all held that the local lesion was attended by vasodilation and hyperæmia, though unable to account for these phenomena apart from the general statement that they were of "sympathetic-tonic" origin. Henschen, Nordström and Rosenbach, and Bum[71] found lesions in the muscles of the painful areas of the face and scalp. The arteries of these areas being sometimes found to have undergone arteriosclerosis, as is well known, the pathological cause of their tendency to remain patent (while those of normal regions contract) is self-evident.

The second, or *vasomotor* form, corresponds with major epilepsy, in that irritation of the vasomotor center is superadded to that of the sympathetic center.[*] It is, therefore, but an aggravated form of that just described. The general blood-pressure being raised, the diseased or lax arterioles allow a still greater quantity of blood to reach the sensory terminals, and the arteries of the painful area are dilated and pulsate strongly, the area itself being deeply congested. The pupil in this form—or stage—of migraine is contracted, the blood having penetrated its arterioles notwithstanding the sympathetic constrictor impulses to them.[*] Hence the greater variety of symptoms witnessed in some cases, spasm of facial muscles, paralysis of the ocular muscles and of the extremities, transient aphasia, etc.

The connection between the sympathetic and vasomotor types is clearly shown by the statement of Gowers,[72] that in some cases, "the pallor gives place to flushing as the pain in the head develops." While admitting, with other neurologists, a vasomotor disturbance, unlike them he regards the latter as of central origin. That engorgement of the local vessels is present is shown by the occurrence of hæmorrhage in some cases—in the orbit, for instance, as in a case reported by Brasch and Levinsohn.[38] "At the end of an attack in which the final dilatation has been marked," writes Gowers, "puffiness of the scalp has been observed in rare cases, and even ecchymoses at the seat of the most intense pain."

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[*] *Author's conclusion.*

[70] Mangelsdorf: Berl. klin. Woch., Bd. xl, S. 1004, 1903.

[71] Bum: Wiener med. Presse, Bd. xxxvi, S. 761, 1895.

[72] Gowers: "Diseases of the Nerv. System," vol. ii, p. 844, 1893.

At the present time the sympathetic and vasomotor forms are interwoven, owing to the prevailing confusion as to the functions of each system as a unit. A clear differentiation of the two forms was, therefore, impossible, and the pathology of the disease has, therefore, remained obscure. Thus Latham states that there is "first of all, *contraction* of the vessels of the brain, and so diminished supply of blood produced by excited action of the sympathetic." So far, I am fully in accord with him. He adds, however, that "the *exhaustion* of the sympathetic following on this excitement causes the *dilatation* of the vessels and the headache." Here, I cannot sustain him, for "exhaustion of the sympathetic" would entail pain wherever the sympathetic fibers govern the peripheral circulation, *i.e.*, over the entire surface. There is no exhaustion, as I interpret the process: certain arterioles are weaker functionally or organically (as is the heart in many subjects) than others; and are unable as well as the latter to resist the centrifugal pressure of the blood, and yield. Hyperæmia of the cutaneous sensory terminals following, pain is experienced. The meninges and brain may likewise become the seat of an hyperæmic area; hence the convulsive seizures sometimes observed in cases of migraine.

Etiology and Pathogenesis.—The principal cause of migraine, *i.e.*, of the excessive vasoconstrictor phenomena to which the attacks are due, is probably paraxanthin, an active poison, and other members of the xanthin group. These intermediate products of metabolism accumulate in the blood between the migrainous attacks, and when the blood attains a certain degree of toxicity, provoke them by irritating the sympathetic and general vasomotor centers.* They accumulate because they are not adequately converted in the blood into benign and eliminable end-products, owing to deficient activity of the anterior pituitary, and, therefore, of a deficiency of auto-antitoxin in the blood.* In most cases this condition is inherited, gouty disorders of the nervous system being readily traceable in proximate ancestors. The majority of cases develop during or after adolescence, when the adrenal system has not kept pace with the general development. In such cases, this system is able to carry on its functions under ordinary conditions; when, however, any unusual stress is imposed upon it by an excess of physiological poisons, it is not equal to the task and they accumulate.* This accumulation may be hastened by indiscretions in diet, excess of food, additional meals such as midnight suppers, entertainment "refreshments," etc. Hence the greater prevalence of migraine among the wealthy classes. A kindred cause is excessive muscular fatigue, a phenomenon also due to the presence of toxic wastes (principally sarcolactic acid) in quantities which cannot be disposed of by the blood sufficiently fast to prevent the development of morbid phenomena.

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* *Author's conclusion.*

[38] Brasch and Levinsohn: Berl. klin. Woch., Bd. xxxv, S. 1146, 1898.

In predisposed subjects attacks may, on the other hand, be evoked by conditions which tend more or less to debilitate the general nerve centers implicated.* Emotional factors, shock, fear, grief, worry, anger, excitement, etc., are familiar exciting causes. Equally familiar are the reflex causes of migraine, eyestrain, nasal and aural disorders, uterine diseases, carious teeth, adenoids and other conditions enumerated as capable also of exciting epileptic seizures, and occupations which entail more or less cerebral hyperæmia, especially intellectual overwork, coupled with inadequate out-of-door exercise.

Rachford[74] has clearly demonstrated that an excess of paraxanthin and other xanthins was present in the urine during and for some time after an attack of migraine, and moreover (1895), that an excessive excretion of paraxanthin coincided with it. This is in accord with the views of French clinicians, Guéneau de Mussy, Bazin, Jaccoud, Labadie-Lagrave, Bouchard and others, who, from the time of Trosseau (who held that "migraine and gout are sisters"), have connected migraine with the so-called "gouty diathesis." Bouloumié,[75] in a study of 1348 cases of gout and kindred disorders treated by him at Vittel, found that the prodromes of migraine frequently occurred as the preliminary manifestations of such disorders, that migrainous attacks appeared especially before and during gouty phenomena, and rarely subsequent to them. Fluctuations in the excretion of uric acid have often been observed and recorded by Haig,[76] a copious elimination of this end-product of metabolism coinciding with the disappearance of the migrainous attack. The pathogenetic process submitted requires no evidence in view of that adduced in the articles on Epilepsy, Eclampsia, etc. The influence of heredity and the connection of eclampsia with epilepsy are well shown by the statistics of Féré—a history of migraine in 232 out of 308 cases of epilepsy.

Treatment.—PROPHYLAXIS.—The general indications, in view of the pathogenesis of the disorder, are (1) to adjust the patient's diet to his assimilative powers, thus reducing to a minimum the toxic wastes formed, and (2) to overcome any condition which, either inherited or acquired, tends to reduce the anterior efficiency of his blood, by inhibiting the functional efficiency of his general nerve centers.[*]

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* *Author's conclusion.*

[74] Rachford: Amer. Jour. Med. Sci., *Loc. cit.*

[75] Bouloumié: Bull. méd. des Vosges, Oct., 1895.

[76] Haig: "Uric Acid as a Factor in the Causation of Disease," 1892.

The first indication is met by reducing markedly the use of highly-nutritious food, late suppers, pastry, red meats and alcoholic beverages being avoided, and meals should be taken at regular intervals. Coffee and tea are harmful, since they raise the vascular tension. Water, however, should be partaken of in large quantities to preserve the blood's fluidity and osmotic properties, and to insure free diuresis. An occasional saline purgative is of service.

The second indication includes the correction of any ophthalmic, nasal, and other condition capable of provoking migraine reflexly.

Liveing,[77] referring to the many distinguished men who suffered from this disorder, states that Marmontel cured himself by eating little, drinking water, taking exercise, and that Haller was equally successful "by drinking every day a large quantity of water, and exchanging a highly nutritious regimen for a much lighter dietary." Linnaeus cured himself by the same means, etc. Patients readily consent to a reduced diet as a rule, but they usually fail to carry out the physician's instructions as to the plentiful use of water. In such cases it is best to order some alkaline water, Ballardvale, Buffalo Lithia, Vichy, etc., and to instruct them to take a glassful at established intervals, one quart being drunk daily. As to reflex causes, according to Lauder Brunton,[78] a careful examination of the eyes, teeth, nose, ears, and throat will reveal some disorder in these organs in practically all cases. This is only mentioned to emphasize the fact that this feature of the treatment should not be neglected.

Preventive remedies should obviously be such as are capable of stimulating the anterior pituitary in order to enhance the proportion of auto-antitoxin in the blood. *Thyroid gland*, 2 grains (0.13 gm.) during each meal, and an occasional saline cathartic are very effective, especially if the patient can lead an out-of-door life.[*] *Potassium iodide*, 5 grains (0.3 gm.) after meals in a large glassful of water, is equally efficacious, and is indicated when any cardiac disorder is present. *Strychnine*, $^1/_{40}$ grain (0.0016 gm.) three times a day, is of signal service, especially when the peripheral circulation is poor, although it tends to stimulate the vasomotor center besides the adrenal center.[*] It is especially valuable also when there is a tendency to melancholia, or mental depression, both frequently observed in subjects predisposed to migraine. In children or adolescents strychnine is advantageously combined when constipation does not complicate the case, with *iron,* especially the dialyzed iron or Blaud's pill.* The dietetic measures recommended should, of course, be carried out simultaneously.

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[*] *Author's conclusion.*
[77] Liveing: "Megrim, Sick-headache, etc.," p. 423, 1873.
[78] Lauder Brunton: Practitioner, Feb., 1894.

The thyroid extract in small doses has given me excellent results, especially in women approaching the menopause, and also where prompt effects were necessary in any case of migraine. Liveing obtained "singular success" from potassium iodide in some cases. J. R. Clemens[79] found it effective in the most aggravated cases. The value of strychnine and iron in such cases is well known. This clearly illustrates the fact that preventive medication in this disorder includes agents which act as "tonics" or, in other words, as stimulants of vital activities through the adrenal system.

Digitalis is indicated when the right heart is dilated, *quinine* when there is history of malarial toxæmia, *sodium salicylate* when gout is a feature of the case or of the history.

Drugs which Reduce Arterial Tension.—When the foregoing measures do not yield the desired result, it is owing to excessive irritability of the sympathetic and vasomotor centers, which causes them to react to the least excitation.* The accesses recur frequently, and the face is usually pale in such cases. *Nitroglycerin* relaxes the entire arterial system, increases diuresis, etc., by reducing the sensibility of the sympathetic and vasomotor centers. Its action should be carefully watched, however, since the recession of blood from the peripheral capillaries tends in itself to inhibit catabolism. For the same reason, the doses should not be too large, 1/[illegible] grain (0.001 gm.) twice daily is ample. It may be used with the thyroid extract, potassium iodide and digitalis, but not with strychnine, which tends to counteract its action.* The *bromide of sodium* can be used instead of nitroglycerin, in hysterical women; but as it tends to inhibit oxygenation when given in large doses or when its use is prolonged, it should only be employed temporarily.

Nothnagel and Rossbach[80] state that the lowering of the arterial tension caused by nitroglycerin is not harmful: "the flow of urine is increased and albuminuria disappears." As the latter symptom is due to excessive vasoconstriction, its disappearance proves that the remedy is beneficial by causing general vasodilation.

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* *Author's conclusion.*

[79] J. R. Clemens: Therap. Gazette, May 15, 1902.

[80] Nothnagel and Rossbach: "Nouveaux éléments de mat. méd. et de thérap.," Paris, 1889.

TREATMENT OF THE ATTACK.—*Drugs which Reduce Arterial Tension.*—Agents capable of producing this effect promptly do not seem to have been tried in migraine; *amyl nitrite* suggests itself as a valuable agent in this connection, provided, however, that the amount inhaled be small, *i.e.*, not more than 5 or 6 drops. *Chloral hydrate* combined with *sodium bromide*, 10 grains (0.6 gm.) of each repeated in two hours, and taken with a wineglassful of water, sometimes wards off an attack. If the pain appears, the local application of *camphor-chloral*, a mixture of the two drugs, equal parts, which forms a viscid liquid, often checks it.

Drugs which Cause Contraction of the Arterioles.—When the arterioles (those which, owing to their failure to contract, allow the blood to penetrate the affected area) are not the seat of sclerosis, stimulation of the sympathetic center will sometimes enforce their contraction, and thus arrest the pain.* *Acetanilid* and *antipyrin* are very effective agents in this connection, 5 grains (0.3 gm.) given every hour three times, usually sufficing to arrest the paroxysm. *Phenacetin* is equally active, but in large doses, *i.e.*, 10 to 15 grains (0.6 to 1 gm.). *Morphine* is eminently an arteriole constrictor, and a subcutaneous injection of $^1/_6$ grain (0.01 gm.) sometimes acts very promptly. Other agents that have a corresponding physiological action, *caffeine*, *guarana*, *ergot*, *cannabis indica*, have been recommended, but their effects vary so greatly, owing probably to the uncertain strength of the preparations available, that dependence should not be placed upon them.

NEURITIS, INCLUDING NEURALGIA, TIC DOULOUREUX, SCIATICA AND ZONA (SHINGLES, HERPES ZOSTER).

Definition.—Inflammation of a nerve, whether termed "neuralgia" or "neuritis," may occur as a result of so many morbid influences, active and passive, that a specific definition cannot be formulated. It is always attended, however, by engorgement of the nerve's arterioles or vasa nervorum and their capillaries, including those of the nervi nervorum, the hyperæmia of the latter and the pressure of the swollen structures surrounding them being the main source of pain.**

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* *Author's conclusion.*
** *Author's definition.*

Symptoms and Pathology.—"Neuralgia," meaning merely pain in the course of a nerve or nerves, is but a symptom of a morbid condition of these structures, and not, therefore, a disease. As it is invariably associated with hyperæmia,* which often progresses to the stage of inflammation, neuralgia is, in reality, but a symptom of neuritis, not only of the incipient stages of this disorder, but also of its advanced stages: *tic douloureux,* for example.*

Dana[54] states that when there is organic disease of the nerve itself, such as neuritis, the disease cannot be, strictly speaking, called neuralgia; and that "it is often impossible to draw the lines absolutely." Some authors limit the term "neuralgia" to cases in which hyperæmia of the nerve is alone present; but there is no legitimate foundation for this interpretation, since, as stated by Dana, "there is hyperæmia with sometimes extravasation of blood" both in interstitial neuritis and perineuritis. Moreover, most acute pain persists even when profound changes of the nerve extending to and involving the ganglion—the Gasserian ganglion in trigeminal neuralgia, for example—are present. Hence the appropriateness of the term "neuralgia" even here—but only when linked with "neuritis."

In the forms of neuritis termed *neuralgia* the pain is sometimes preceded by numbness or stiffness, or conversely by soreness, tingling or throbbing in the affected area, but, as a rule, it appears spontaneously. At first, it is generally intermittent, and may be sharp, stabbing or burning in character, and be localized or extend throughout the entire length of the nerve. The paroxysms, which vary greatly in intensity, occur at irregular intervals of a few minutes in mild cases, and may then only recur after considerable time. When simple hyperæmia has lapsed into inflammation, however, intense pain—usually worse at night—may persist days, weeks, months, etc., *i.e.,* until the cause is eradicated.

While at first the surface of the affected area may present some numbness, or be normally sensitive, the region becomes hyperæsthetic when inflammation of the nerve is impending or is present, especially where the nerve overlies a hard muscle, or passes over the edge of a bony opening, the supraorbital foramen, for instance. The painful area is often infiltrated, swollen and red. In simple hyperæmia, firm pressure often relieves the pain, but the same procedure greatly augments the pain when active inflammation is present.

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* *Author's conclusion.*

[54] Dana: "T. B. of Nerv. Dis. and Psych.," sixth edition, p. 158, 1904.

The pain is due to congestion of the minute capillary networks in the peri- and endoneurium, the larger vessels of which are arterioles supplied with sympathetic fibers. Congestion of these arterioles and capillaries gives rise to pain by causing swelling of the nerve and pressure upon the nervi nervorum, which are themselves hyperæmic, and, therefore, hypersensitive.*

The nervi nervorum, the existence of which was shown by Horsley, terminate in minute bulbs similar to the tactile end-bulbs of Krause, and are, therefore, sensory. Weir Mitchell and Marshall concluded that the pain of neuritis and neuralgia was due to pressure upon these delicate sensory organs. That hyperæmia is the source of this pressure, is suggested in many ways. As Gowers[illegible] says, "we know that in all organs, vascular dilatation attends functional activity." That hyperæmia—a result of vascular dilatation—is the cause of neuralgia, *i.e.*, nerve-pain, is likewise recognized. In neuritis, the case is the same. Tyson,[illegible] for example, states that "an inflamed nerve is reddish, from hyperæmia of the *vasa nervorum*, though the stage of demonstrable hyperæmia may have passed away when the nerve comes under observation." This coincides with the definition of Dana previously given.

Each of the two disorders included in the term neuritis-neuralgia has been divided into special varieties, the principal of which are *tic douloureux,* trifacial or trigeminal neuralgia, sciatica, the regional neuralgias and multiple neuritis.

TRIFACIAL NEURALGIA OR TIC DOULOUREUX.—This is the most painful of the entire series, and is the most common. The *ophthalmic division* of the fifth is that most frequently affected, the familiar supraorbital neuralgia. The pain, which may radiate to the inner angle of the orbit, the eye and lids, the eye-ball and the corresponding side of the nose and head, is apt to recur at stated periods morning or night. Lachrymation, conjunctival congestion, local flushing, sweating and swelling, are often observed. The least effort increases the pain, each pulse-beat causing an exacerbation. Such an access may last one or more hours, and cease spontaneously, to return perhaps after a few weeks or months, or it may steadily grow worse and cause many years' excruciating suffering.

Next in order is the *superior maxillary division,* the tender point of which is at the intraorbital foramen, the pain radiating to the malar bone, over the cheek, the corresponding side of the nose, and some of the upper dental nerves. Less common is that of the *inferior maxillary division,* with two tender points, one at the mental foramen, the other just in front of the ear, the pain extending over an extensive area in some cases, *i.e.,* the preaural region, the tip of the tongue, the lower jaw, the inferior dental branches, the ear, the temple and the parietal eminence.

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* *Author's conclusion.*
[illegible] Gowers: *Loc. cit.*
[illegible] Tyson: *Loc. cit.*, p. 367, 1905.

The primary changes in the affected nerves are hyperæmia, as stated, but in cases in which the neuralgia persists, inflammation occurs, owing to disease of the neural arteries.

Dana[54] long ago contended that many cases, at least, are due to arteritis. In five cases of trigeminal neuralgia, he found no noteworthy changes in the nerves, while in three there was marked arterial disease. Putnam[55] likewise found, in some instances, the intima of the blood-vessels greatly thickened. Thoma,[56] Rose[57] and Keen and Spiller[58] and others have all found a marked increase in the size of the vessels, the two former in segments of peripheral nerves derived from cases of trifacial neuralgia, the last-named authors in Gasserian ganglia derived from similar cases.

Even the axis-cylinders, which, as I have pointed out, are channels for the blood's oxidase, are engorged: Stengel,[59] referring to neuritis, says, for instance: "In the acute forms partially degenerated fibers with fatty myelin-sheaths and swollen axis-cylinders, are found very early." Again, Spiller found swollen and irregular axis-cylinders and small vessels in some of the Gasserian ganglia resected by Keen. Of one of these he says, referring to the axis-cylinders: "In most portions of the field, these appear as drops of a red, hyalinelike substance," doubtless methæmoglobin and adrenoxidase.

SCIATICA.—The pain usually starts in the upper part of the sciatic nerve in the gluteal region immediately behind the great trochanter, and follows the course of that nerve, radiating downward into the popliteal space and thence to the internal malleolus and the dorsum of the foot. It is usually very acute, and is increased by the least motion. By raising the limb bodily, thus producing flexion at the pubis, Lasègue's sign is elicited: a violent pain along the entire sciatic. There is marked tenderness over the latter, especially between the ischium and the great trochanter. Sometimes there is fever at the outset. There may be muscular tremor, a forerunner of atrophy of the muscle, or œdema. The skin of the region may then be pale and glossy, its temperature being also reduced. An eruption identical to that of herpes zoster occasionally develops along the course of the nerve. The positions assumed by the patient when standing, sitting, etc., are all calculated to favor the diseased limb.

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[54] Dana: Med. News, May 16, 1891.
[55] Putnam: Boston Med. and Surg. Jour., Aug. 13, 1891.
[56] Thoma: Deut. Archiv f. klin. Med., Bd. xliii, S. 409, 1888.
[57] Rose: Trans. Med. Soc. of London, vol. xv, p. 157, 1892.
[58] Keen and Spiller: "On Resection of the Gasserian Ganglion," Phila., 1898.
[59] Stengel: "T. B. of Pathol.," third edition, p. 831, 1900.

Sciatica is a neuritis from the outset, the primary infiltration, due to the accumulation of colorless blood-plasma in the nerve, being the initial phenomenon of an inflammatory process, which, like all forms of "neuralgia" and neuritis, may culminate in degenerative changes in the nerve.

Sciatica is the only "neuralgia" in which exception might be taken as to its being a neuritis. Thus, while Herter[60] ten years ago referred to sciatica as a neuritis, *i.e.*, as "an *inflammation* of the great sciatic branch of the sacral plexus," Dana, in the last edition of his text-book, says that "a large proportion of the cases is due to a neuritis." In the light of my views, sciatica is a neuritis in all cases, since the exceptions are all attended with hyperæmia, the first stage of inflammation. Again, "hyperæmia" is generally supposed to be denoted by redness of the neural structures involved, but we may have hyperæmia without redness, since, as I have shown, the blood-plasma that circulates in the terminal neural capillaries, including the axis-cylinder, does not contain red corpuscles. Indeed, if we term this fluid "serum" (of which the *extra corpore* serum is but chemically-altered semblance) it is possible to trace the inflammatory process from its incipiency to that of clearly defined trophic lesions. This is facilitated by a review of the literature embodied in a paper by J. Ramsay Hunt.[61] In a case in which Cotugno[62] found *œdema* of the nerve-sheath "15 c.c. ($^1/_2$ ounce) of *serum* was removed by puncture." Martinet[63] "described the nerve as *œdematous* and of *reddish hue*, with hæmorrhages into the sheath" in one case and as "infiltrated with *serosanguineous* fluid" in another. This evidently refers to the continuity of the nerve, for Gendrin,[64] in a case of fifteen days' duration, found the nerve-trunk "*reddened*, swollen, and the seat of serous infiltration down to the popliteal space. All this is due, of course, to engorgement of the vessels and exudation of the blood-serum: In a case of fifteen days' duration recorded by Fernet,[65] in which the nerve-trunk was greatly swollen, "the *nerve* was of reddish hue and the *vessels* of the neurilemma were injected." Though the nerve, examined microscopically by Déjerine and Raymond, showed no structural alteration, Fernet held that a neuritis was present. The advanced stage is shown in Ramsay Hunt's own typical case, in which the various parts of the nerve showed concomitantly the various stages of the process: a translucent, jelly-like substance in the epineurium and marked thickening and sclerosis of the larger vessels of the epineurium and perineurium and the smaller vessels of the endoneurium, with "small extravasations of blood" in "the loose areolar tissue of the sheath at all levels examined." The "thigh and leg had undergone a slight but visible atrophy" there were also twitchings and paræsthesia.

This exemplifies the morbid process in trigeminal neuralgia, since similar lesions were found in the Gasserian ganglia removed by Keen, and studied histologically by Spiller. The first-named author states that "the medullary substance of the nerve-fiber within the ganglion" was "immensely swollen, atrophied or entirely gone;" and that the vessels were "distinctly sclerotic," etc.—the sequence of events observed in all cases of "neuralgia" so-called, in which the morbid process has progressed sufficiently far.

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[60] Herter: Dercum's "T. B. on Nervous Dis.," p. 849, 1895.
[61] J. Ramsay Hunt: Amer. Medicine, Apr. 15, 1905.
[62] Cotugno: "A Treatise on Sciatica," London, 1775.
[63] Martinet: Thèse de Paris, 1818.
[64] Gendrin: "Histoire anat. des inflammations," Paris, 1826.
[65] Fernet: Arch. gén. de méd., 7ième. série, vol. 1, p. 382, 1878.

NEURITIS OF THE HEAD, NECK AND TRUNK.—Besides the most common of all neuralgias, the trigeminal, already described, there is a variety due essentially to eye-strain, *i.e.*, the *ocular neuralgia,* usually limited to the eyeball. The pain may be quite severe, and radiate to the forehead over the frontal sinus. In *cervico-occipital neuralgia,* the pain starts behind the mastoid process, radiates posteriorly to the upper part of the neck and in front and above to the parietal eminence. The main nerves involved are the posterior branches of the upper four cervical. In *intercostal neuralgia* the pain starts from the spinal cord end of the intercostal nerves from the third to the ninth, and radiates round the chest; it is often very severe and is increased by motion, respiration and coughing. An eruption similar to that of herpes zoster occurs in many cases. *Pleurodynia* is, strictly speaking, neuralgia of the pleural nerves; it resembles the pain of acute pleurisy, and is very severe, especially during expansion of the chest. *Gastrodynia, enteralgia, hepatalgia, nephralgia, mastodynia, coccygodynia,* etc., are defined by their names.

In all these forms, with the exception of the cases of intercostal neuralgia in which the herpetic eruption occurs, the neural hyperæmia rarely exceeds the stage of plasmatic engorgement, the pain, as stated, being due to pressure upon the nervi nervorum.

HERPES ZOSTER (*Shingles, zona*), the form commonly witnessed, is but an intercostal neuralgia in which the inflammatory process, which often includes the ganglion of the affected nerve, has advanced beyond the preliminary plasmatic hyperæmia. The typical eruption—a reddish patch which soon develops into a crop of œdematous vesicles—may occur in any part of the body, wherever "neuralgia" has been observed. Dull pain in the affected region usually precedes by a few days the eruption and the acute pain, which develops suddenly and is extremely sharp, burning, and lancinating, in adults. The site of the eruption becomes markedly hyperæsthetic, the contact of the clothes being unbearable. It is nearly always unilateral, though it frequently reaches beyond the middle line of the body in the "intercostal" form, and lasts from ten days to two weeks. The lesion may be hæmorrhagic, ulcerative, gangrenous, etc., and may be followed by persistent local neuralgia, anhydrosis or hyperhydrosis, muscular atrophy, etc. In some cases there is considerable fever, showing a tendency to intermittence, and especially marked towards evening.

The kinship of this disorder with the ordinary neuralgia is well shown by the large proportion of cases of trigeminal zona in Greenough's[96] and Cantrell's[97] statistics. Any part of the body in which innervation is impaired and where neuralgia is known to occur, may become the seat of herpes zoster. Hence the so-called "trigeminal," "femoral," "brachial," "ophthalmic," etc., forms which constitute the "regional" zosters. Guermonprez and Platel[98] observed it repeatedly on the fingers. The pathology of zoster also identifies it as a pure neuritis. W. F. Robinson[99] states that "Daniellsen found the intercostal nerve reddened and thickened and the neurilemma markedly infiltrated," and that the more recent investigations have shown that "the ganglion is not alone the part that is first attacked, but that the inflammation may arise at any point in the continuity of the nerve-trunk in its peripheral termination in the spinal cord or within the brain." Robinson's own investigations showed the presence of "a perineuritis of the cutaneous nerves exhibiting a small-celled infiltration of the neurilemma" —a condition witnessed early in sciatica.

NEURITIS OF THE EXTREMITIES.—The most important of the series is sciatica, reviewed above. *Cervico-brachial,* and particularly *brachial neuralgia,* are counterparts of sciatica. Jointly, they include the area supplied by the brachial plexus, *i.e.,* the four lower cervical nerves and the greater part of the first dorsal. The radial and ulnar are the nerves most frequently affected, the main tender points being at the elbow over the ulnar, and at the wrist over the inferior ulnar. The axilla and the shoulder are also the seat of tender points when the upper segments are involved. There is usually a dull, continuous, toothache-like pain along the entire course of the nerve or nerves affected, but with violent exacerbations or paroxysms of a stabbing, lacinating character. Temporary loss of power is often observed, and muscular atrophy may follow severe cases. As in sciatica, the skin may become glossy and thin, and is somewhat œdematous in most instances. As in sciatica also, there is inflammation of neural structures.

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[96] Greenough: N. Y. Med. Jour., Oct. 19, 1889.

[97] Cantrell: Phila. Med. Jour., Mar. 26, 1898.

[98] Guermonpres and Platel: Jour. des mal. cutan. et syph., vol. xi, p. 721, 1899.

[99] W. F. Robinson: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. iii, p. 462, 1899.

Femoral, or *crural, obturator, plantar, metatarsal* and other forms of neuralgia are described, all of which differ as regards the area involved, but the pathology of which (that of a more or less advanced neuritis) is always the same, *i.e.,* that of an inflammatory process.

Musculospiral neuritis, owing to the superficial position of the musculospiral nerve, is not infrequently observed. The pain —though the disorder is not termed a "neuralgia" in text-books —is very severe, and the local tenderness is equally marked. This applies likewise to *median neuritis,* the intense pain radiating to the first two fingers and the thumb. Precisely as a flexure of the thigh in sciatica provokes severe pain throughout the entire nerve, so does a stroke on the end of one of the painful fingers cause a flash of pain up the whole length of the median. *Ulnar neuritis, brachial neuritis, circumflex neuritis,* and the many other varieties of *true* neuritis likewise provoke pain and other symptoms and trophic lesions common to the various forms of neuralgia reviewed.

General Pathology.—In all forms of true neuritis, the congestion may originate from two directions: (1) from the arterioles that enter the nerve from the side by piercing the perineurium, and whose capillaries form networks in the endoneurium to *nourish* the nerve; (2) from the axis-cylinders themselves, whose neuro-fibrils, as I have pointed out, are channels for plasma laden with adrenoxidase, which, by reacting with the phosphorus-laden constituents of the myelin, gives rise to the nerve-energy, *i.e.,* the impulse along the whole nerve, including its terminals.*

Any inflammatory lesion of the nerve-fiber itself, *i.e., parenchymatous neuritis,* must entail, therefore, phenomena ascribable to impairment of the nerve's conductivity: muscular atrophy, paræsthesias, cutaneous lesions, etc. Identical disorders may be produced, however, by pressure of the connective tissue forming partitions around nerve-bundles when these partitions are the seat of congestion, *i.e.,* perineuritis, but only when this is marked, the pressure being caused by the engorged arterioles or their capillaries and the serous exudation derived from the latter. This pressure is also, we have seen, the source of pain, the nervi nervorum being compressed, while the infiltration accounts for the œdema. When the local lesions assume a morbid trend or the nerve is beyond repair from the start through local injury, the granules of adrenoxidase in the axis-cylinders remain unused and accumulate,* and the myelin sheath breaks up into droplets. Finally, these are absorbed and the field is invaded by lymphocytes, and finally occupied by their product, *i.e.*, newly formed connective tissue—the terminal sclerosis.

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* *Author's conclusion.*

This normally leads to the conclusion that *true* neuritis is primarily a vascular disorder of the perineural and interstitial connective-tissue framework of the nerve, and that the nutritional disorders of the muscles, skin, etc., are due to pressure by engorged vessels, serous effusion, etc., upon, or destruction of, the nerve-fiber bundles (axis-cylinders) which these inflamed structures surround.

This does not mean that the cell-bodies in the central ganglia, from which the compressed axis-cylinders arise, may not themselves become involved in the morbid process. When they do, however, it is through an ascending neuritis, the destructive inflammation extending towards the cerebrospinal axis and gradually destroying the ganglion itself.

That the axis-cylinders of a nerve receive a part of their blood through their cell-bodies in the organ from which they originate,* was shown in a preceding chapter. The importance of this fact finds its practical application in the present connection. It furnishes a sound foundation for the—now established—clinical difference between the neuritis of individual nerves and multiple neuritis.* This is clearly defined by McPhedran[380] in the following lines: "In isolated neuritis the disease begins in the nerve-sheath, constituting a 'perineuritis,' the inflammation extending to the nerve-fibers afterward. In the multiple forms the nerve-fibers themselves are the seat of the primary change, the sheath becoming affected later." The latter, as will be shown in the next heading, I do not regard as a form of "neuritis." The fact that a neuritis steadily ascends from the periphery has been noted by several investigators. Thus, Sydney Schwab,[381] after a study of 20 recorded instances, including two of his own in which the Gasserian ganglion had been examined microscopically after extirpation, concluded that disease of the nerve-cells did not exist as a primary parenchymatous affection, and that in trigeminal neuralgia two classes of phenomena could be distinguished, namely: (1) an ascending neuritis *beginning at the periphery* and having a tendency to ascend to the ganglion; (2) an interstitial inflammation, chronic and progressive, of the ganglion itself. Moreover, Rose[382] found the lesions more marked at the peripheral ends of diseased nerves than at their central ends. All these observations have been confirmed repeatedly.

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* *Author's conclusion.*

[380] McPhedran: Med. News, Oct. 21, 1899.

[381] Sydney Schwab: Annals of Surg., June, 1902.

[382] Rose: *Loc. cit.*

Etiology and Pathogenesis.—Although the causes of *true* neuritis, including the "neuralgias," are very numerous, the pathogenesis is the same in every instance, *i.e.*, some primary physical interference with the normal functions of the nerve.* We may thus have neuritis due to mechanical injury of the nerve, as from blows, contusions, wounds, stretching (as in dislocations, fractures, etc.) and pressure, the latter including compression by aneurysms, tumors, crutches, sleeping upon the arm, etc., and excessive use of an extremity. The lesion is essentially local and what degree of neuritis occurs is associated with an attempt at repair.* This applies likewise to the extension of localized disease, carcinomatous, syphilitic, tuberculous or other foci, or tumors, caries of bone, etc. In any of these, destruction of the nerve may lead to trophic disorders, paralysis, etc., differing in no way from those observed in trigeminal and other severe neuralgias.

In 30 cases of Morton's disease, *i.e.*, metatarsal neuralgia, Robert Jones[103] traced 10 clearly to injury. Neuralgia of various nerves of the arm, due to excessive professional use of this member, was observed in 30 cases by Bernhardt;[104] leeching over the nerves was found to give marked relief in some cases—evidence that hyperemia and neuritis, therefore, were the cause of pain.

The lesion is primarily local also in the most frequent cause of neuritis: exposure of a part of the body, one side of the head and face, the neck, the gluteal region, etc., to a draught of cold air, especially while the area exposed is warm, flushed and perspiring. The arterioles of the cutaneous tissues being suddenly chilled while dilated, the temperature of the auto-antitoxin is reduced, thus inhibiting the action of its trypsin, and two sets of morbid phenomena occur: (1) temporary paresis of the local arterioles; (2) temporary inhibition of the proteolytic process through which the local waste-products of metabolism are reduced to eliminable end-products.* We are dealing here with a neuritis, since the morbid dilation of the neural arterioles necessarily entails hyperæmia of the perineurium and engorgement of the endoneurium, and pressure, therefore, upon the *nervi nervorum*. In addition to this passive hyperæmia, the region becomes the seat of the active hyperæmia incident upon the reparative process, including the destruction of detritus.* Hence the severity of the pain in neuralgia.

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* *Author's conclusion.*

[103] Robert Jones: Liverpool Med.-Chir. Jour., vol. xvii, p. 1, 1897.

[104] Bernhardt: Semaine médicale, vol. xvi, p. 12, 1896.

As in migraine, neuralgia may be due to reflex action owing to some ocular, aural, nasal, cutaneous or other lesions.

The pathological anatomy of the local lesions we have seen is invariably connected with local congestion. This controverts a prevailing misconception of the manner in which neuralgic pain is provoked, viz., that it can be caused by a deficiency of blood in painful areas, or by "poisons" circulating in the nerve. Even in joints, the accumulation of endogenous poisons does not provoke pain directly; were it otherwise, it would be impossible to account for the disappearance of pain under the influence of hot, dry air, and other measures which do not destroy chemically the poison directly. But the action of hot, dry air is readily explained—as well as the beneficial effect of heat in neuralgia—when we recall that the activity of the blood constituents—the ferment in particular—which destroy the toxics is enhanced by heat.* The need of the antitoxic inflammation being reduced, the local hyperæmia is correspondingly diminished, and pain is reduced in proportion. In other words, it is not the poison which causes the pain, but the reparative process which the presence of the poison engenders, and particularly the congestion it entails.

Neuralgia frequently occurs irrespective of any apparent exciting cause, such as a cold, a traumatism, etc. The causative neuritis appears almost invariably after puberty, in subjects debilitated by physical or mental overwork, infectious diseases, malaria, prolonged lactation, or by the prolonged ingestion or absorption of certain poisons, alcohol, lead, arsenic, etc. Here, the neuritis is secondary, in the sense that it is evoked as a complication of another, but general, disorder.*

The debilitating influences mentioned react on the general organism, we have seen, by reducing the functional efficiency of the anterior pituitary body.* In a large proportion of cases the inefficiency of this organ is inherited, "neuralgia" being often observed in families in which epilepsy, hysteria and other nervous diseases have prevailed. Entailing as it does, a reduction, more or less marked, of the blood's properties, poisons of autogenetic origin such as those that occur in the blood in gout, rheumatism, uræmia and kindred conditions, are allowed to accumulate in the blood-stream. Hence the frequent association of both neuritis and "neuralgia" noted by clinicians.* When this accumulation of physiological poisons has reached a certain degree, the phenomenon witnessed in epilepsy, migraine, etc., occurs, viz., a violent reaction of general centers of both lobes of the pituitary, including those of the sympathetic and vasomotor systems.*

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* *Author's conclusion.*

Important in this connection is the fact that the intestinal canal takes an active part in the morbid process, the inadequate evacuation of excrementitious materials causing it to act as a source of autoinfection. There is usually constipation and the stools are exceedingly foul. The underlying cause of this is an imperfect disinfection of the intestinal contents by the succus entericus, *i.e.*, by the auto-antitoxin it contains,* the result, we have seen, of insufficiency of the adrenal system.*

The kinship between neuralgia, migraine and epilepsy extends even to the characteristic symptoms of the latter disease. Gowers, for instance,[105] refers to two cases of neuralgia attended with vomiting; to another in which opisthotonos was "so severe that the patient rested on the head and the heels." Anton[106] also observed two cases in which attacks of trigeminal neuralgia lapsed into typical epileptic seizures. Grinker,[107] on the other hand, reported a case in which right trigeminal neuralgia coincided with neuritis of the left sciatic, etc. Féré[108] and others have emphasized the analogy between certain forms of neuralgia, the *tic douloureux*, for instance, and epilepsy. In Putnam's[109] opinion, that difference between neuralgia and migraine is one of degree rather than of kind. Lange[110] has called attention to the frequency of the alternation of migraine with neuralgia.

The pain is limited to a given area, and recurs in that area because its vessels have, some time in the course of the patient's life, been exposed to one or more of the many exciting causes capable of bringing on an attack, cold, traumatism, pressure, etc. These exciting causes evoking, as stated above, an inflammatory process in the walls of the neural vessels, this process forms the starting-point of the endarteritis and arteriosclerosis found, we have seen, in advanced cases.* When, therefore, the accumulated blood-poisons provoke, by irritating the sympathetic and vasomotor centers, a rise of the blood-pressure of the entire body, the neural blood-vessels of the "neuralgic" area yield more readily than those throughout the rest of the body, and the nerve becoming hyperæmic, pain is provoked.

We have seen that in epilepsy and migraine there is primarily a general constriction of the arterioles, because the sympathetic center is the first stimulated; and that this is succeeded by general vasomotor constriction when the vasomotor center yields to the irritation. The case is the same in neuralgia. The great influx from the ventral vessels to the periphery which attends general vasoconstriction soon overcomes the resistance of the weakened arterioles of the affected area and enforces their dilation. Although it has so far remained unexplained, this sequence of events has been actually witnessed. Thus, Gowers states that the first effect is usually "a constriction of the vessels of the part" and that "this is often followed by their relaxation."[*]

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* *Author's conclusion.*

[105] Gowers: *Loc. cit.*, vol. ii, p. 800, 1893.

[106] Anton: Wien. klin. Woch., Bd. ii, S. 221, 1889.

[107] Grinker: Jour. Amer. Med. Assoc., July 15, 1905.

[108] Féré: Revue de médecine, vol. xii, p. 497, 1892.

[109] Putnam: *Loc. cit.*

[110] Lange: Hospitalstidende, p. 521, 1891; Satellite of the Annual of the Univ. Med. Sci., Mar., 1892.

Treatment.—Neuralgia, especially the trigeminal and sciatic forms, involves so much suffering that the first indication is to control the pain. In the light of the pathogenesis of neuritis described in the foregoing pages, this reduces itself to the use of measures calculated to diminish the congestion of the neural blood-vessels, and thus to reduce the pressure upon the nervi nervorum. The next indication is to remove, if possible, the cause of the disorder itself.

Measures which Reduce the Congestion of the Painful Area.—The majority of cases observed in general practice occur in subjects predisposed to frequent recurrences. Even the worst form of neuralgia, tic douloureux, is characteristically prone to remissions, of days', weeks', and even months' duration. The pain, therefore, cannot be ascribed to the permanent lesions in the nerve itself; it must be due to some *fluctuating* agency:[*] the local hyperæmia, we have seen. It is not only therefore in mild cases that reduction of the local congestion is indicated, but also in the worst cases. To accomplish this, we have at our disposal four groups of remedies:—

(1) Drugs which cause general vasodilation by depressing directly the general vasomotor center.[*]

The *bromides* are useful agents of this class in mild cases. In the average case, however, they are unreliable, unless large doses are used, when gastric disorders, bromism and accumulation of toxic wastes in the blood are likely to follow. By giving small doses—10 grains (0.6 gm.)—and using the sodium salt, these drawbacks are reduced to a minimum, while its analgesic properties may be increased by means of *chloral hydrate*, 10 grains (0.6 gm.), the central action of which is similar to that of the bromides. The combined use of these two salts, every two hours, aided by one of the local remedies enumerated below, usually masters the mild forms commonly

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[*] *Author's conclusion.*

*observed. When the pulse is tense and hard, especially in plethoric subjects, a third vasomotor depressant, **veratrum viride**, may be added, 2 drops* (or four times this amount: *1905 U. S. P.) of the tincture being given every two hours.* When no heart lesion is present, the pain may be relieved by the inhalation of three drops of *amyl nitrite,* in the physician's presence. Five or six drops poured on absorbent cotton in an emery-stoppered bottle, affords the patient a convenient and safe means, through which he can obtain relief by taking an occasional "whiff." The preliminary use of amyl nitrite—which also lowers arterial tension—followed by the bromide-chloral mixture, generally proves more satisfactory, however. *Nitroglycerin* advantageously replaces the latter agents in many cases, especially when large nerves, those of the brachial plexus and the sciatic, for instance, are inflamed. It depresses both the vasomotor and sympathetic centers,[*] and by thus reducing the vascular tension in all vessels, counteracts the pressure in the hyperæmic nerves, and bleeds them, as it were, into the great central trunks. In trifacial neuralgia, the pain may be increased at first through the dilation of the arterioles; but this does not occur after a few doses of the bromide-chloral mixture.[*] The dose, one minim of the 1-per-cent. solution gradually increased to four minims, three times daily. While nitroglycerin is often curative, the bromides, chloral and amyl nitrite are only temporary expedients which should be withdrawn after cessation of the pain.

The influence of general vasodilation is well illustrated by Pommerol's case,[111] in which a sciatica of five years' standing was cured by the bite of a viper. The value of nitroglycerin has been recognised by Herter,[112] Mikhalkine,[113] Lawrence, Krauss[114] and others.

(2) Drugs which cause general constriction of the arterioles by stimulating the general sympathetic center.[*]

Of this group, the coal-tar products are the most effective, especially *acetanild* in 5-grain (0.3 gm.) doses every hour three times, then every three hours, until the pain ceases. By causing powerful constriction of the peripheral arterioles, they reduce greatly the proportion of blood supplied to the inflamed nerves;* the latter being simultaneously depleted in the veins, the pressure upon the nervi nervorum ceases and the pain likewise. *Phenacetin*, in 10 to 15 grain (0.6 to 1 gm.) doses, is also useful. *Antipyrine* is more apt to provoke untoward effects than acetanild, but it has proved valuable especially in sciatica, when injected, with an equal quantity (10 grains—0.6 gm.) of sterilized water, in the tissues immediately overlying the nerve. The coal-tar products should be used only temporarily as analgesics. *Morphine* relieves pain in the same way, whether administered orally or subcutaneously close to the diseased nerve. Deep injections, practically down to the nerve, of $^1/_6$ grain (0.01) morphine and $^1/_{120}$ grain (0.0005 gm.) *atropine* are very effective, even in sciatica. This should be repeated daily. When there is reason to believe that a drug-habit may be initiated by using the foregoing drugs internally, the same physiological effects may be obtained with *aconitine*, $^1/_{400}$ grain (0.00015 gm.) every four hours, gradually increased until the first "physiological" effect, *i.e.*, tingling, appears, when the dose should be somewhat decreased. The tincture of *aconite* root (1905 U. S. P.) 4 minims (0.25 gm.) may be used instead if preferred; it is especially effective when given with the tincture of *gelsemium*, 10 minims (0.6 gm.), given every hour, until the labial and digital tingling of aconite is felt. These two remedies sometimes prove curative. *Cocaine* also relieves pain by causing constriction of the arterioles. It has given good results when injected in doses of $^1/_4$ to $^1/_2$ grain (0.016 to 0.03 gm.) in solution, over the seat of the pain. In neuralgia of the face it may be injected into the arm, carefully avoiding a vein. *Osmic acid*, which acts similarly, is sometimes very effective in severe cases, when 10 to 20 minims (0.6 to 1.2 c.c.) of a 1-per-cent. solution are injected near the nerve, or better into its substance after exposing it surgically.

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[*] *Author's conclusion.*

[111] Pommerol: Gaz. des hôpitaux, Aug. 2, 1900.

[112] Herter: *Loc. cit.*

[113] Mikhalkine: Med. Obosrenie; Revue de thérap. médico-chir., vol. lxii, p. 122, 1895.

[114] Krauss: N. Y. Med. Jour., Feb. 29, 1896; Buffalo Med. Jour., Oct., 1897.

Cocaine has also been used in sciatica in the form of intrarachidian injections, but the ordinary methods are as effectual. The danger of penetrating a vein was suggested by Bergmann,[115] who, having obtained immediate relief in a case of sciatica by injecting 15 minims (0.90 c.c.) of a 5-per-cent. solution of cocaine, without observing the least untoward effect, caused violent symptoms of intoxication the next

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[*] *Author's conclusion.*

[115] Bergmann: Münch. med. Woch., Bd. xlvii, S. 392, 1900.

day in the same patient by an injection of only 5 minims (0.3 c.c.) of the same solution. As recommended by Cagney,[126] cocaine should be used with prudence. Osmic acid has been recommended by many observers since Billroth suggested its use over twenty years ago. J. B. Murphy,[127] G. A. Wright,[128] and others, now expose the nerve in rebellious trifacial neuralgia under anæsthesia, and inject from 5 to 10 minims (0.3 to 0.6 c.c.) of a 1.5-per-cent. solution into the nerve-substance and between the nerve and its sheath. This is thought to cause degeneration, the pain ceasing permanently in most cases.

(3) Local remedies which produce reflex constriction of the peripheral arterioles, including those of the painful nerves, by irritating directly the cutaneous sensory terminals.*

Aconitine acts in the same way, applied locally, in the form of an ointment composed of 4 grains (0.25 gm.) of the alkaloid, 2 drachms (8 gms.) of glycerin, and 6 drachms (24 gms.) of cerate; *veratrine*, 10 grains (0.6 gm.), may be added for severe cases. Care should be taken to avoid rubbing this ointment over an abrasion, since it is violently poisonous. *Ethyl chloride* sprayed over the painful region daily sometimes proves curative. The skin should be protected by a thin layer of grease. In mild cases *menthol* rubbed freely on the skin is quite effective. Its efficiency is greatly increased by the addition of guaiacol; 15 grains (1 gm.) of each may be dissolved in 5 drachms (20 gms.) of absolute alcohol, and rubbed gently over the congested nerve. Again, *cocaine*, 15 grains (1 gm.), may be combined with menthol, 10 grains (0.6 gm.), in one drachm of vaselin, and rubbed into the skin with a wad of cotton. *Chloral hydrate*, with equal parts of *camphor*, forms a thick liquid which, painted freely over the affected region, serves often to prevent the pain until internal treatment has controlled the cause. *Galvanism*, the anode well moistened with salt water, being placed over the painful spot, also relieves pain by causing constriction of the vessels that supply the nerves.

(4) Measures which provoke direct or indirect depletion of perineural arterioles, and, therefore, of the endoneural capillaries.*

Guaiacol is so active in this connection that 15 drops applied to the skin have caused a marked decline of the peripheral temperature, and even prostration. Equal parts of guaiacol and glycerin painted over the diseased nerves promptly relieves pain.

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* *Author's conclusion.*

[126] Cagney: Provincial Med. Jour., Apr. 1, 1895.

[127] J. B. Murphy: Jour. Amer. Med. Assoc., Aug. 22, 1903.

[128] G. A. Wright: Med. Chronicle, Feb., 1904.

Leeches afford a ready means for direct depletion; but in brachial neuritis *bleeding* may be resorted to with advantage, the abstraction of a few ounces of blood sufficing. *Cupping* is still recommended by some eminent neurologists. *Hydrochloric acid* painted over the nerve, three or four times at 48 hours' interval, affords effective counterirritation in neuralgia of the extremities. *Superheated dry air* is very effective, not only because it draws blood to the skin, which becomes quite red, but because the activity of the auto-antitoxin of the blood is greatly enhanced.* *Warm pack* about the abdomen or even the ordinary hot water applied over this region markedly facilitates the action of any drug administered internally calculated to deplete the congested area. *Heat* applied to the latter in the form of the hot-water bag, a hot brick, a hot hop or bran bag are familiar derivatives which assist the curative process also by increasing catabolic activity of the trypsin in the auto-antitoxin.*

MEASURES WHICH TEND TO ELIMINATE THE CAUSE OF THE NEURAL CONGESTION.—Of the many exciting causes of neuritis enumerated, those that belong to the domain of the physician are closely allied, we have seen, (1) to disorders, such as migraine, gout, epilepsy, etc., which are attended by an accumulation of toxic wastes in the blood, and (2) with intestinal torpor due to the same central cause, and entailing auto-intoxication. Since the pain occurs in most cases as intermittent paroxysms caused by the accumulation of toxic materials in the blood, measures which prevent the latter should prevent the return of the pain.

In some cases purgatives now and then suffice to prevent the accesses. *Castor oil,* of all remedies of this class, has given the best results in 1 to 2 ounce (28 to 56 gm.) doses each morning. Mixed with two or three tablespoonfuls of ale (preferably Bass's, owing to the large quantity of gas it contains) it forms an emulsion and cannot be tasted. After the first few days it causes but one evacuation daily. The oil causes both catharsis and disinfection by increasing reflexly the relative proportion of auto-antitoxin in the intestinal juice.* *Citrate of magnesia* and other saline purgatives taken occasionally, only prevent the attacks in mild cases, and require the aid of remedies that stimulate the adrenal system. The *dietetic* measures recommended for migraine[119] are also indicated in cases of neuralgia when at all severe. This applies likewise to the use of *saline solution* when the general symptoms point to a considerable accumulation of toxic wastes in the blood, especially in sciatica. In all such cases the free use of *pure water* as a beverage is very beneficial, while the use of alcohol, coffee, and tea is harmful.

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* *Author's conclusion.*

Castor oil has given excellent results in the various forms of neuralgia. Ochsner reported 13 cases all materially improved. Moyer[120] treated 15 cases in the manner outlined in above text. Of seven reported but one failed to be benefited, four being cured. Aldrich,[121] Waxham[122] and others, have also recommended this treatment. Debove and Bruhl[123] found a saline solution composed of 5 per mille each of sodium chloride and sodium sulphate, effective in sciatica.

Of the drugs which have been used to controvert the "gouty" state—by stimulating the adrenal system—*sodium salicylate,* or *salicin,* 5 to 15 grains (0.3 to 1 gm.) in cachets, followed by a glassful of water, has given good results, but both agents sometimes cause gastric disorders. A more satisfactory remedy is *strychnine* in full doses, $^1/_{40}$ grain (0.0016 gm.), gradually increased to $^1/_{20}$ grain (0.0032 gm.) three times daily. It powerfully stimulates the anterior pituitary body, thus enhancing the oxidizing power of the blood, and is especially active in early cases, and when anæmia is present. In sthenic cases *sodium iodide* in 10 grain (0.6 gm.) doses in a large glassful of water after each meal is more effective. It may be gradually increased, but as soon as any sign of iodism appears the doses should be reduced as needed to avoid this phenomenon, the smaller dose being continued. When gout or rheumatism is present *colchicum,* 10 minims (0.6 gm.) of the tincture, increases greatly the efficiency of the iodide; *colchicine,* $^1/_{120}$ grain (0.00054 gm.), may be used instead of the tincture. *Quinine* is often recommended, but it is really beneficial when malaria underlies neuritis and when anæmia is present. In sthenic cases, it causes hypertonicity and increases the pain. The *benzoate of sodium,* 5 grains (0.3 gm.) every three hours the first two days, then after each meal, is often efficacious in children or young adolescents.

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[119] *Cf.* this vol., p. 1536.

[120] Moyer: Jour. Amer. Med. Assoc., Apr. 21, 1900.

[121] Aldrich: Cleveland Med. Gaz., Nov., 1900.

[122] Waxham: Colo. Med. Jour., Dec., 1901.

[123] Debove and Bruhl: Gaz. des hôpitaux, vol. lxviii, p. 365, 1895.

In neuralgia as well as migraine, the case should be carefully examined lest the pain be reflex. Any causal disorder of this kind should, of course, be eliminated. This being done and the measures recommended failing to remove the suffering, surgical measures should be resorted to, especially in *tic douloureux*. In this acutely painful form of neuralgia, the best operation so far devised is that of division of the sensory root of the fifth nerve, a safer and more efficacious operation than removal of the Gasserian ganglion.

Strychnine in heroic doses was found effective by Dana[134] in cases of one or two years' duration. It arrested the disease almost invariably. In cases of six or seven years' duration and in those in which inflammatory changes—especially scleroses—were present, no benefit resulted. It is usually given hypodermically, but as more than one injection can hardly be administered daily, a large dose has to be given. I have found it more advantageous to give it internally as stated, *i.e.*, in divided doses, since a larger aggregate of the drug can thus be used.

Division of the sensory root of the fifth pair for *tic douloureux* has recently been perfected by Frazier and Spiller, who introduced this operation. In the four cases reported[135] there had been no recurrence of the pain, the longest time elapsed being two years and eight months, and the shortest fourteen months. It entails much less hæmorrhage than removal of the Gasserian ganglion, is less dangerous, avoids ocular disturbances and particularly ulceration of the cornea.

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[134] Dana: Jour. Amer. Med. Assoc., May 5, 1900.

[135] Frazier and Spiller: *Ibid.*, Oct. 1, 1904.

CHAPTER XXVI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

DISORDERS DUE TO HYPERACTIVITY OF THE ADRENAL SYSTEM.

Although the above heading would appear to incriminate the adrenal system as the source of the disorders considered in this chapter, the morbid effects its excessive functional activity engenders are, in truth, primarily due to the presence in the blood of one or more poisons which overstimulate the test-organ, and thus cause an excessive production of adrenoxidase. As I will show in the following pages, it is this agent which, by enhancing metabolism inordinately in the walls of the arterioles of the vasa vasorum, causes the lumen of these vessels to become obliterated. Atheromatous degeneration thus becomes but a normal result of the fact that the nutrition of the vascular tissues supplied by these minute vessels is prevented.

This points, however, to the adrenal system as the dominant factor of arteriosclerosis, a disease which, although as stated by Sir James Barr,[1] "kills more men in the prime of life and vigor of manhood than any other," is far from being understood. Indeed, Joseph Collins,[2] after a comprehensive study of the subject, was recently led to conclude that "there is no unanimity of opinion concerning the way in which the morbid condition constituting arteriosclerosis develops." The adrenal system fulfills quite as prominent a position in the pathogenesis of the two main results of arteriosclerosis, viz., angina pectoris and cerebral hæmorrhage, as we will presently see.

ARTERIOSCLEROSIS.

SYNONYMS.—*Atheroma; Arteriofibrosis; Endarteritis Chronica Deformans.*

Definition.—Arteriosclerosis is primarily due to the presence of endogenous or exogenous toxic substances in the blood, in excess of the quantity which the auto-antitoxin[*] of the latter can convert into benign and eliminable end-products. The adrenal system being kept overactive by these poisons, however, the proportion of adrenoxidase in the blood is excessive, and the walls of all vessels are the seat of inordinate metabolic activity. This may cause either abnormal constriction of the vasa vasorum, and thus impair vascular nutrition, the denourished areas becoming the atheromatous or sclerotic patches; or, it may initiate the latter by increasing the digestive or proteolytic activity of the defensive ferments, thus causing destruction of the blood elements and autodigestion or autolysis of the vascular tissues.

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[1] Sir James Barr: Brit. Med. Jour., Jan. 20, 1906.
[2] Collins: N. Y. Med. Jour., June 9, 1906.

Symptoms.—Although arteriosclerosis gives rise to symptoms that vary according to the organ which is the seat of the most advanced lesions, there are certain phenomena that are common to all cases. Before the characteristic vascular lesions are discernible, these cases are apt to show evidences of general asthenia, being readily fatigued by exertion, and sweating readily without adequate cause. The face is pale, especially about the mouth, temple and eyes, and a tendency to giddiness and loss of intellectual acumen is occasionally observed.

When the disease is sufficiently advanced, the characteristic symptoms are eminently vascular. Prominent among these is the resistance of the vessels to pressure, especially discernible when the finger is applied over the arteries of the wrist and popliteal space. The resistance may be due to two factors: one of these, increase of tension of the vessel, is not always present, and often occurs in other diseases; while the other, thickening of the vessel-walls, is a characteristic sign when high tension is alone present, firm pressure arresting the pulsations beyond the seat of pressure. When the artery is sclerosed, however, this cannot be done, the vessel's pulsations being quite perceptible notwithstanding the compression; the pulsation is also prolonged owing to the narrowing of the vascular lumen. High tension and sclerosis are often present simultaneously; in that case, the signs of sclerosis prevail. Another sign is usually present to confirm the diagnosis: a tortuous, dilated, and pulsating appearance of the arteries of the temple. Sphygmographic tracings show a short sloping upstroke, a wide top and a slow, gradual downstroke. The pulse is usually slow and retarded at the wrist when the narrowing of the artery is marked, and may differ on the two sides if the stenosis of one vessel is more marked than that of the other arm. Another confirmatory sign is often present, *i.e.*, the *arcus senilis.*

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[*] *Author's definition.*

Early in the course of the disease the urine is apt to be more abundant and to show variations of specific gravity. Albuminuria may then appear intermittently, and finally contain casts. When these organs are seriously involved, anuria and the symptoms of chronic fibrous nephritis may appear and symptoms of uræmia likewise. Arteriosclerosis of the uterus is sometimes the cause of severe hæmorrhage at the menopause or in aged subjects. In the latter the bleeding is difficult to control, owing to the arterial fibrosis. The dislodgement of thrombi, due to endarteritis, or detached thrombi or widespread arteriosclerosis, sometimes gives rise to gangrene of the extremities.

An important feature of the whole problem is the asthenic character of the disease emphasized by many authors, whether met in a decrepit old subject or in an overfed gourmand. Thus Stengel[3] includes among the earlier symptoms "reduced vitality," and remarks that "many cases of neurasthenia are of cardiovascular origin," and characterizes as the "arteriosclerotic facies," "a peculiar pallor" specially conspicuous around the mouth, temples and eyes. Kisch[4] associates obesity with arteriosclerosis.

Bittdorf,[5] as shown farther on, associates marked pallor with aortic arteriosclerosis. As to the involvement of the uterus, Reinicke[6] observed four cases of this kind in which hysterectomy became necessary to avoid a fatal issue. The vessels of the organ showed typical lesions of the senile type. Similar instances have been reported by Cholmogoroff,[7] Grube[8] and others. Ergot invariably aggravates the bleeding.

The *heart* finally becomes hypertrophied, owing to the increased resistance of the blood-column. The left ventricle having to bear the brunt of the increased work, however, it is the one which undergoes hypertrophy first; the aortic second sound is therefore unusually accentuated, clear and ringing. This is best heard behind, over the angle of the left scapula on a level with the seventh dorsal spine. This unilateral enlargement and the unusual displacement the increased vigor of the left ventricle entails tend to displace the heart as a whole—the apex being sometimes over an inch or more nearer the sternum than usual. This hypertrophy is a desirable condition, and serves to overcome the obstruction to the blood-stream. The general health may not be impaired by its presence a number of years therefore, until the coronary arteries are markedly diseased and the nutrition of the myocardium is seriously compromised. When this occurs degeneration of the heart-muscle supervenes with its consequences: heart-failure, arhythmia, dyspnœa, pulmonary congestion, œdema, etc. Angina pectoris is a formidable complication of the lesions of the coronaries, though not due, as now believed, to obstruction of these vessels, but, as shown farther on, to their inability to control the volume of blood admitted into the pericardium.* Rupture of the heart-wall may occur, with hæmorrhage into the pericardium.

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[3] Stengel: Amer. Medicine, Jan 2, 1904.
[4] Kisch: Wiener klin. Rundschau, Bd. ix, S. 371, 1895.
[5] Bittdorf: Deut. Archiv f. Med., Bd. lxxxi, S. 65, 1904.
[6] Reinicke: Archiv f. Gynaek., Bd. liii, S. 430, 1897.
[7] Cholmogoroff: Monats. f. Geb. u. Gynaek., Bd. xl, S. 692, 1902.
[8] Grube: *Ibid.*, Bd. xvi, S. 258, 1902.

Hasenfeld[9] found in the course of extensive pathological studies that arteriosclerosis only leads to hypertrophy of the left ventricle when the splanchnics or thoracic aorta are severely affected. Arteriosclerosis of the other vessels does not seem to have such an effect. Runsberg[10] holds, on good ground, that the cardiac symptoms are of dual origin, the one set arising from the sclerosis of the coronaries, the other due to impairment of the cardiac functions owing to the sclerosis of the vascular system at large. Stengel very appropriately states that arhythmia in persons near forty is too often attributed to gastric disturbances, tobacco, tea, coffee, etc.

The *aorta* is often involved, and tends greatly to aggravate the patient's general condition. The face is often very pale and there is a marked tendency to obesity. Abnormal pulsations in the subclavian and carotid arteries are usually marked, and dilation of the veins of the chest may sometimes be provoked by forced respiration; the tissues over the sternum will then appear œdematous as in aortic aneurism. The pupils may differ in size, though the reflexes remain normal, and the retinal vessels may be dilated and even hæmorrhagic. Respiratory phenomena are of frequent occurrence, there being a tendency to bronchitis, emphysema, bronchiectasis and hæmoptysis, with a marked susceptibility to tuberculosis. A prominent symptom is weakness of the arms. The resistance to the blood-stream being increased in the aorta, the cardiac hypertrophy attending the general disease is aggravated, and may even occur if the aorta be alone the seat of the characteristic advanced lesions. While the first aortic sound is clear and distinct, the second sound is more or less accentuated. The peripheral vessels may show but slight arteriosclerosis. The pulses of both sides often differ, and the pulse is generally rapid, though the blood-pressure be increased. Palpitations, cardiac oppression and dyspnœa are caused by exertion, while vertigo, tinnitus and other symptoms of the general dyscrasia may appear.

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* *Author's conclusion.*

[9] Hasenfeld: Deut. Archiv f. klin. Med., Bd. lix, S. 193, 1897.

[10] Runsberg: Finska Läk. Handl., Bd. xliii, Nu. 6, 1900.

The symptomatology of aortic arteriosclerosis has recently been carefully worked out by Bittdorf[11] in 54 cases not complicated by aortic stenosis, aneurism, coronary sclerosis or nephritis. The symptoms outlined in the general text are mainly those given by this investigator. William Welch[12] states that the aorta is a region of predilection for the cicatricial form of arteriosclerosis. It shows but little tendency to extend into the large branches of the aorta or into the abdominal aorta. The changes occur in the adventitia and media, and may consist of furrows and depressions, elevated plaques or fibrous scar-like patches.

Arteriosclerosis of the *brain* is a prominent feature of many cases. Vertigo is a salient symptom of this condition, especially in the aged. In these and younger subjects the early manifestations may assume the form of intellectual torpor with loss of memory for recent events, irritability and darting head-pains. Aphasia, somnolence, tinnitus aurium, inequality of the pupils and disorders of vision and sensation, *i.e.*, insecurity of gait or even numbness of one limb or one side of the body. Apoplectiform and epileptiform attacks, preceded by the characteristic prodromes, are sometimes witnessed in such subjects, and, in fact, may precede those just outlined. Senile dementia or general paralysis which occasionally occur are due, in keeping with the other phenomena, to degenerative changes.

In a study of 200 cases of apoplexy M. Allen Starr[13] found that 80 per cent. showed many of the above phenomena as prodromal signs. Hence the importance of recognizing them early so as to foretell, if possible, the apoplectic attack. Joseph Collins,[14] in an able article based on a study of 800 cases of arteriosclerosis, states that "the most striking feature of the disease is the alteration of the patient's appearance. The individual becomes transformed from a person expressing grace in movement and relaxation in repose, into an immobile, inanimate replica of the normal person" . . . . "the gait is perhaps the most remarkable feature of the patient. The stride is short, oftentimes only a few inches, the feet widely separated and not lifted from the ground, the rhythm of the movement often slow and rapid." In 15 advanced cases Zapinsky[35] found cortical vascular lesions in 14. Collins states that the most striking alterations are found in the middle cerebral arteries and the branches. In some instances the entire brain is shrunken. Bondurant,[36] after a study of 200 cases, concludes that "the characteristic and ever-present mental expression of arteriosclerosis is dementia of some kind or degree."

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[11] Bittdorf: *Loc. cit.*
[12] William Welch: N. Y. Med. Jour., June 18, 1904.
[13] M. Allen Starr: Med. Record, July 4, 1903.
[14] Joseph Collins: N. Y. Med. Jour., June 9, 16, 23, 1906.

Arteriosclerosis of the *spinal cord* and *peripheral nerves* may act as the underlying cause of numerous diseases of these organs. Lesions of the lower half of the cord evoke morbid phenomena in the lower extremities; lesions of the upper half in the upper, or in both upper and lower. If the anterior horns are involved, motor symptoms appear; if the lesions are located in the posterior horns, the disorders are sensory. Besides these territorial effects, however, the specific symptomatology of arteriosclerosis asserts itself. Thus, besides gradual development of paralysis of the lower extremities, preceded by stiffness, muscular cramps, etc., the arteries show the typical signs; the blood-pressure is high and the characteristic heart-sounds are present.

The spinal type of neurasthenia, pain in the back, numbness of the legs, irregular twitchings of the muscles and weakness, irregularity in urination, and constipation and various forms of neuralgia are also witnessed.

Joseph Collins, referring to the symptomatology given in outline in the first paragraph, and illustrated by a typical case seen with Zabriskie, states that when advanced, such cases are often diagnosticated as transverse myelitis or chronic myelitis. He refers to an instance in which the symptoms came on so abruptly that the diagnosis of Landry's paralysis was made. He states also that it was well described by von Leyden (1875), who looked upon it as a senile process in the spinal cord. The neurasthenic type outlined in the second paragraph is regarded by M. Allen Starr[37] as due to malnutrition of the cord.

Pathogenesis and Pathology.—In the majority of cases of arteriosclerosis, the disease is preceded by a general adynamia due to functional torpor or hypoactivity of either of the organs of the adrenal system, or all of them, *i.e.*, the adrenal center, the adrenals or the thyroid.* This may be the result of normal or premature senility, starvation, or of diseases such as syphilis and influenza, which depress markedly the functional activity of the adrenal center;* or of poisons such as alcohol, phosphorus

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* *Author's conclusion.*

[35] Kapinsky: Wratch, No. 4, p. 95, 1896.

[36] Bondurant: Intern. Med. Mag., July, 1896.

[37] M. Allen Starr: *Loc. cit.*

—that of the endotoxin of tuberculosis, for example—which deoxidize the blood and thus render all the organs of the adrenal system hypoactive;* or of inherited functional debility of this system.*

Old age is not a cause of arteriosclerosis. The organs of the adrenal system becoming senile with the rest of the organism, the process of life which they govern, *i.e.*, tissue metabolism, is inhibited in proportion. The other etiological factors are generally recognized as such. Moritz,[18] in a study of 100 cases of arteriosclerosis under 60 years of age (Russians), found that 47 gave a history of syphilis acquired from eight to thirty years before the date of examination, and that all but four were immoderate or moderate consumers of alcohol. Though this applies to Russian lower classes and cannot be taken as standard for people of other countries, the potent influence of syphilis and alcohol is, nevertheless, illustrated. Sir J. Barr[19] regards syphilis as the most potent factor in the production of arteriosclerosis, and holds that typhoid fever plays a considerable part in its induction. Excessive smoking is also believed to be pathogenic. Boveri[20] produced atheroma of the aorta in the rabbit by the administration per ora of an infusion of tobacco. Nammack[21] attaches great importance to heredity as an etiological factor. Bock[22] attributes a certain proportion of cases to insufficient food.

In this group of cases the exciting causes of arteriosclerosis are toxic products of hypocatabolism, including xanthin and hypoxanthin, which are present more or less continuously in the blood, owing to the functional torpor of the adrenal system.* Hence* the fact that the gouty diathesis is generally included among the causes of arteriosclerosis.

The poisonous properties of xanthin, hypoxanthin and other toxic wastes of the purin group were first shown, we have seen, under Gout, by Grancher and fully confirmed by Kolisch, Tandler Paltauf and Albrecht. Croftan,[23] moreover, showed that they produced granular degeneration of the epithelium of the convoluted tubules and proliferation of the endothelium of the intertubular epithelium. The corresponding lesions in the smaller vessels in arteriosclerosis, in the familiar "endarteritis obliterans," the "arteriolitis" of Letulle, etc., correspond with these processes,—all inflammatory in nature, as pointed out by Virchow in 1856, precisely as the lesion in the kidneys, the interstitial nephritis leading to contraction, is inflammatory.

Gout is now generally considered as a cause of arteriosclerosis, whereas, as interpreted from my standpoint, the etiology of gout and that of arteriosclerosis are—as far as the xanthin group is concerned—similar, *i.e.*, adrenal insufficiency leading to the formation of toxic wastes as a preliminary feature. Rachford,[24] nearly ten years ago, emphasized this kinship and attributed the main phenomena witnessed in arteriosclerosis to xanthin and other purin bodies. "We can well imagine," says this author, "that this condition of the arteries might result from their long-continued irritation by the presence of an excess of the alloxuric bodies in the blood," several cases being adduced in support of this view. If the multiplicity of conditions with which arteriosclerosis is associated, migraine, neuralgia, neuritis, asthma, etc., are compared to those associated with the gouty diathesis, the strength of this interpretation will appear. Again, we have seen in the article on Gout that, as first shown by Levison, the kidneys are profoundly diseased in gout. The similarity of the lesions in both diseases, however, may be illustrated by Osler's statements that in gout[25] there is "an interstitial nephritis, either the ordinary 'contracted kidney' or the arteriosclerotic form," and that in arteriosclerosis,[26] "the condition is practically that of contracted kidney."

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* *Author's conclusion.*

[18] Moritz: Med. Examiner, Oct., 1904.

[19] Sir J. Barr: *Loc. cit.*

[20] Boveri: Clinica medica, No. 6, 1905; Gazz. d. Osped. e delle Clin., vol. xxv, pt. 1, p. 666, 1905.

[21] Nammack: Med. Record, Oct. 28, 1901.

[22] Bock: Zeit. f. diät. u. physik. Ther., Bd. ii, S. 33, 1898.

[23] Croftan: Jour. Amer. Med. Assoc., July 8, 1899.

[24] Rachford: Phila. Med. Jour., Apr. 18, 1896.

Arteriosclerosis differs from gout and the diseases that are provoked by the gouty diathesis in that it may be caused (indirectly) by poisons other than the purin bases. Thus it may be caused by products of tissue catabolism, such as those derived from the muscles during violent exertion or physical labor, or from the brain tissues during excessive mental strain, or from the combination of these two factors which constitutes "strenuous life." The disease may also be provoked by the pathogenic elements of many infectious diseases, typhoid fever, variola, erysipelas, pneumonia, measles, scarlatina, acute rheumatism, septicæmia, etc., and various poisons such as lead.

Excessive muscular exertion is regarded as a prominent predisposing factor. Thayer and Brush,[27] in an analysis of nearly 4000 patients suffering from various diseases, found the percentage of palpable radial arteries materially higher among individuals in whom there was a history of heavy physical labor. Collins[28] states that "within the present generation arteriosclerosis has advanced from the position of a senile manifestation and a necessary accompaniment of old age, which our predecessors had given it, to one of the commonest sequences of the strenuous, disordered life."

The toxic origin of arteriosclerosis has been pointed out by Traube, Rokitanski and many others. Both Huchard and Runeberg ascribed endarteritis to a toxin in the blood. Thérèse[29] was able to prove this fact experimentally. Gilbert and Lion,[30] Boinet and Romary[31] and others produced atheroma of the aorta by injecting various pathogenic bacteria. A comprehensive study of the question also led Russell[32] to conclude that the disease is due to the presence of deleterious substances in the blood. Again, Flexner[33] observed a case in which the aorta had apparently been rendered tuberculous through infection of the intima by the blood-stream—a legitimate conclusion in view of my contention that the endotoxin of tubercle bacilli acts through the phosphorus it contains. Thayer and Brush,[54] in 21 out of 52 autopsies in typhoid fever, found fresh patches in the aorta, and in 13 out of 62 autopsies, similar patches on the coronary arteries.

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[25] Osler: "Principles and Practice of Medicine," third edition, p. 411, 1898.

[26] Osler: *Ibid.*, p. 775.

[27] Thayer and Brush: Jour. Amer. Med. Assoc., Sept. 10, 1904.

[28] Collins: N. Y. Med. Jour., June 9, 1906.

[29] Thérèse: Thèse de Paris, 1891.

[30] Gilbert and Lion: C. r. de la Soc. de biol., 9 série, vol. 1, p. 583, 1889; Arch. de méd exper., vol. xvi, p. 73, 1904.

[31] Boinet and Romary: *Ibid.*, vol. ix, p. 902, 1897.

[32] Russell: Lancet, June 1, 1901; Feb. 7, 21, 1903; and Brit. Med. Jour., June 4, 1904.

[33] Flexner: Johns Hopkins Hosp. Bull., Aug., 1891.

These poisons provoke arteriosclerosis by causing an excessive or too prolonged defensive reaction of the adrenal system.* The blood being supplied with an excess of adrenoxidase, the muscular coats of all vessels, including those of the nutrient arteries of the latter, the vasa vasorum, are subjected to excessive metabolism, which causes them to remain more or less permanently constricted, and finally to hypertrophy, thus obliterating the vessel.*

The marked vascular tension observed in many cases of arteriosclerosis—which constitutes one of its most dangerous phases, owing to the danger of arterial rupture, cerebral hæmorrhage, aneurism, etc., it entails—is the subjective manifestation of this condition.* The arterioles which supply the vasa vasorum being primarily affected in this manner, owing to their diminutive size, the areas of the vascular coats to which they are distributed are no longer adequately nourished; they finally become necrotic, therefore, and are then transformed into atheromatous or sclerotic patches.*

Russell[55] has urged the existence of a close connection between arteriosclerosis and vasoconstriction, the latter being attributed by him to the presence of poisons in the body, *i.e.*, to autointoxication.

The vasa vasorum have long been known to play an important rôle in the process. Cowan[56] states, in fact, that the "vasal changes may, in some cases, be the only visible lesion," and refers to cases in which "the interference with the vascular supply from the vasal vessels produced medial and intimal necrosis." Osler, referring to Councilman's study of 41 autopsies, states that "in the circumscribed or nodular arteriosclerosis the primary alteration consists in a degeneration or a local infiltration in the media and adventitia, chiefly about the vasa vasorum." All this applies to the large vessels as well as to the aorta. Cowan states that he has witnessed obliterating lesions in the aortic vasa after acute rheumatism.

Interesting experiments have shown recently that injections of a solution of adrenalin during a prolonged period produced typical atheromatous lesions. This fact, first observed by Josué, has been confirmed by Gouget,[57] R. M. Pearce and E. MacD. Stanton[58] and L. Braun.[59] The latter observer, however, injected amyl nitrite simultaneously to counteract the vasoconstrictor action of the adrenalin. As the arterial sclerosis followed nevertheless, he concluded that its action was similar to that of other toxics. This view is in accord with my interpretation of the mode of action of the adrenal secretion: By injecting persistently adrenalin (the active principle of this secretion) into the blood, they produced excessive intracellular metabolism, constriction and obstruction of these vessels in the experimental animals. In most cases the pathogenesis may be divided into three types: the *adrenal* type just described, the *autolytic* type, and finally, the *denutrition* type.

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* *Author's conclusion.*

[54] Thayer and Brush: *Loc. cit.*

[55] Russell: *Loc. cit.*

[56] Cowan: Practitioner, Mar., 1906.

[57] Gouget: Presse méd., vol x, p. 896, 1906.

[58] R. M. Pearce and E. MacD. Stanton: Albany Med. Annals, Feb., 1906.

[59] L. Braun: Wiener klin. Woch., Bd. xviii, S. 150, 1905.

As to the *autolytic type,* the pancreas, from my viewpoint, plays one of the leading parts in the process. Besides governing carbohydrate metabolism, it supplies a ferment or ferments which take a direct part in the protein metabolism of the tissue cells, and also in the defensive reactions within these cells, as well as in the phagocytes and blood-stream.

We have seen that the presence of trypsin and other ferments in leucocytes is now recognized as a fundamental feature of phagocytosis. Metchnikoff's cytase is regarded by him as a tryptic ferment. We have also seen that some leucocytes, at least, migrated from the intestinal canal to the tissue cells, there to carry on, among other functions, that of catabolism, besides acting as phagocytes in the blood. These cells were shown to take part in the defensive process in the plasma when it was invaded by bacteria, toxins, toxic waste products, or other substances harmful to the tissue cells, the catabolic phase of metabolism here serving to break down the pathogenic substances, endogenous or exogenous, precisely as it did wornout components of the tissue cell.

Abderhalden[illegible] has since reached very similar conclusions. "Everything points," writes this observer, "to the fact that the [tissue] cell has agents at its disposal which render it capable of splitting up into their simplest units all the complicated substances which are brought to it or which it itself builds up." Again, "Each separate cell with very few exceptions disposes of the same or similar ferments as those secreted by the digestive glands in the intestinal canal." As to the manner in which the tissue cells are reached by these ferments, he writes: "Many facts accord with the suggestion that the leucocytes play a part in connection herewith." In keeping with my own views, Abderhalden has termed the digestive ferment a "defensive ferment," thus bringing, he adds, "the so-called reactions of immunity into close line with processes that are normal and consequently familiar to the cells." Briefly, the same process which prepares foodstuffs for assimilation and breaks them down to eliminable wastes is used by Nature to convert pathogenic substances likewise into eliminable end products, thus protecting the organism against their morbid effects. This conception of immunity, while devoid of complexities, enables us to understand clearly many patho-

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[illegible] Abderhalden: "Defensive Ferments," 3d Ed., 1914.

logical and clinical phenomena that have remained unexplained. In arteriosclerosis, and other conditions, we witness, among other causative phenomena, exaggeration of this digestive process, with tissue destruction as a result.

As to the digestive ferments, their presence in tissue cells has long been recognised. No less an authority than Vaughan states[illegible] that "the cell which can no longer supply a digestive ferment is already dead, whatever be the kind or amount of pabulum surrounding it." Of the presence of the digestive ferment in the blood, E. L. Opie[illegible] writes: "The ability of the blood to remove injurious material is dependent on the possession of proteolytic enzymes. Peculiar to the polymorphonuclear leucocytes is an enzyme which, like trypsin, exerts its digestive action in an alkaline medium."

Wheeler and Bishop's sensitization theory of arteriosclerosis is also based on the presence of trypsin in the tissue cells, with excess of proteins as the main pathogenic agent.

Yet how is this sensitizing process carried on and how are the arterial lesions provoked? We are not dealing here with a sudden anaphylactic reaction, but, in practically every instance, with a very slow and gradual erosion, as it were, of the vascular walls. How is this morbid process developed? This is where, I believe, the functions of the thyroid and adrenals assert their influence. While there is no proof that the protein itself activates directly the trypsin zymogen in the cells, much evidence is available to show that it does so indirectly by evoking, in the body at large, a defensive reaction.

The protein enhances the functions of the thyroid and adrenals beneficially up to a certain limit, harmfully when this limit is exceeded. In other words, proteins used in excess awaken a reaction having for its purpose the conversion of the harmful surplus of proteins, both in the cells and in the blood, into eliminable end products. As long as the excess is only such as to keep this protective reaction within certain bounds, no harm to the tissue cells results, even though the cellular proferment is sensitized; but if, when the protective tide is at its highest level, more proteins are added and the already sensitized cellular proferment becomes activated it digests the cell itself, starting the destructive process, or autolysis, the precursor of arteriosclerosis.

The sensitizing properties of the thyroparathyroid secretion, which I assimilated to those attributed to opsonin by Sir A. E. Wright, has been confirmed by others. For the chemical process involved, I may recall that the high liver in the early stages of arteriosclerosis often presents symptoms of Graves's disease, flushing, sensation of heat, nervous irritability, palpitations, high blood-pressure, etc., and that the thyroid gland or its preparations do not always produce vasodilatation, as is

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[illegible] Vaughan: Amer. Jour. Med. Sc., Feb., 1912.

[illegible] Opie: Arch. of Int. Med., June, 1910.

generally stated. W. E. Waller[43] has also emphasized this fact recently, citing a number of cases of Graves's disease in which, in keeping with some of my own observations, the blood-pressure rose to 170, and in one instance to 250 mm. Hg. In the present calamitous war hyperthyroidia has also been found by L. T. Thorne[44] to be accompanied by a rise of blood-pressure. Autopsies of victims of Graves's disease often show, moreover, arterial degeneration presenting the characters of arteriosclerosis.

The thyroid and adrenal secretions being admittedly increased by protein in excess, the rise of temperature awakened enhances the digestive activity of cellular ferments.

That the thyroid influences oxidation is well shown by the studies of Magnus-Levy, Salomon, Steyrer, and others, in which among other conclusive facts, the intake of oxygen in Graves's disease was found to be increased from 50 to 80 per cent. As regards the adrenals, the progressive fall of temperature from normal to 80° F. or even below, which follows their extirpation, the low temperature attending Addison's disease and the fact that, as stated by Biedl,[45] injections of adrenalin may cause a considerable rise of temperature, point to the influence these organs have on general oxidation—a process which I regard as the most important of their functions. Finally, that the thyroid and adrenals act jointly and are mutually necessary is well shown by the observation of Eppinger, Falta, and Rudinger, that adrenalin fails to raise the blood-pressure after the thyroid has been removed.

Recalling the stimulating influence of overfeeding, particularly of protein wastes, on the thyroid and adrenals, and that the excessive activity of these organs so raises the sensitiveness of the cellular trypsin that this ferment tends to digest the very cells which harbor it through, as we now see, increased oxidation, we are brought to realize how typhoid fever, scarlatina, influenza, rheumatism, tuberculosis, and other febrile infections may initiate the disease. Alcohol belongs to the same category as a cause since it is by undergoing oxidation in the body that it liberates its energy. The cases due to the excessive use of tobacco probably belong also to this class, Cannon, Aub, and Binger[46] having found that injections of nicotine in small amounts in cats caused an increase of adrenal secretion. Gley likewise observed recently that nicotine caused an increase of adrenalin in the blood, while in rabbits Leo Loeb found that the primary lesions caused by nicotine were in the intima.

As to the pathological lesions produced, the blood being the active oxidizing agent, the lesions are those of the nodose type, affecting first the intima, particularly where the blood is most rich in glandular products, and then the aorta, where autolysis is most active.

The third or *denutrition type* imposes itself, when we take into account the fact that cases of myxedema frequently show *post-mortem* advanced arteriosclerosis with typical lesions including calcification.

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[43] Waller: Practitioner, May, 1912.
[44] Thorne: London Lancet, June 15, 1916.
[45] Biedl: "Internal Secretory Organs," p. 226, 1912.
[46] Cannon, Aub, and Binger: Jour. of Pharmacol. and Therap., Mar., 1912.

A similar condition has been observed by Bourneville, Marchand, Heyn and others, in hypothyroidia, while premature arteriosclerosis is not uncommon in diabetes, particularly in the advanced stage. The influence of the thyroid apparatus upon oxidation and metabolism explains this phenomenon—diminished functional activity, obviously defective metabolism, and degeneration in the vessel walls. The sclerosis, fibrosis, or calcification found more or less in all forms being a process of local repair, it occurs as well in this degenerative form as it does in the two preceding.

In the aged, arteriosclerosis is due in some instances to deficient activity of the ductless glands.

As shown by the studies of Landau,[47] Ecker, Heine, Rolleston, and others, the adrenals, for instance, show marked reduction in volume and in wealth of vascular channels and secretory activity in aged individuals. This applies also to the thyroid.

The fact that hypoactive adrenals do not prevent the development of this denutrition type of arteriosclerosis, suggests that high blood-pressure is not necessarily a feature of the morbid process. Indeed, various observers have brought on the disease by injecting toxins, including adrenalin with agents, amyl nitrite, for instance, which would prevent a rise of blood-pressure, or in doses too minute to affect the latter.

High blood-pressure should be regarded more in the light of a very important early symptom and also as a valuable danger signal in advanced cases than as a causal factor of the disease, bearing in mind, however, that in some patients it is compensatory.

Treatment.—If the death rate of arteriosclerosis and its many complications is to be reduced materially, the symptomatology of the presclerotic stage should be established as clearly as possible, *i.e.*, the stage before the blood-vessels have become the seat of lesions, when either excessive adrenal activity, autolysis, or arterial denutrition is taking place. The etiology here is of cardinal importancce. As to the symptoms of fully developed disease, they are virtually similar, being those of arterial degeneration, however caused.

Adrenal Type.—Although Josué and others recognize a clearly defined adrenal syndrome, both the prodromic and late signs they describe may occur in the autolytic period as well. In cases of sustained exertion, as in laborers, letter carriers, bicyclists, etc., the adrenal factor may be discerned to a certain extent. The blood-pressure is apt to be somewhat high, 150 mm. Hg or thereabout; the patient may complain of headache or rather of fullness about the brow and of cramps in the calves of the legs. He may be irritable or, conversely, exuberant, flushed and buoyant, "feeling like being on the go all the time," as one patient expressed it. The pulse may be slow and full and the heart beat, though normal, somewhat forcible. Epistaxis and conditions which the patient defines as nervousness, palpitations, sleeplessness, especially during the early morning hours, a nervous or hacking cough, asthenia or a "wheezing under the breast bone," and often gastric disorders in which hyperchlorhydria and pyrosis are prominent signs. In fact, it is usually for some gastric derangement with constipation or for muscular pains attributed to rheumatism that the patient presents himself.

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[47] Landau: St. Petersburg Med. Woch., June 14, 1908.

Such men may, in keeping with what is observed in hypernephroma, show great muscular development—sufficient in three patients whom I have seen to suggest larval acromegaly—and perspire very freely. They may also show venous engorgement, venous pulse, facial congestion, all symptoms of hyperadrenia, all due to thickening of the arterial coats, especially of the muscular media. Conversely, they may appear pale, complain of cold extremities, and stand cold weather badly. This may be due to constriction of the peripheral arterioles, but in all likelihood is due to the onset of organic lesions.

Such cases yield readily to measures calculated to reduce the functional activity of the adrenals. A *less arduous occupation* and *abstention from meat, coffee, tea,* and *alcohol* to lower the vascular tension often suffice. If the vascular tension is high, the conditions of the kidneys should be looked into. As a rule at this time, these organs are found normal though some polyuria may be present. *Spirit of nitrous ether* may then be used in small doses three times daily to reduce the tension if it fails to recede after a few days, and also small doses of *sodium bromide* and *chloral* on retiring if the tendency to insomnia persists.

The iodides at this stage are harmful. So are strychnine, digitalis, and tonics in general, most of which stimulate the adrenals and aggravate the trouble.

Autolytic Type.—This type may either begin with the symptoms described, where the causative poison is one acting slowly, as is the case in the large proportion of patients in whom the disease is due to the excessive use of proteins, alcohol, coffee, etc., or may follow a febrile disease. Here, we are no longer dealing with erethism due merely to exaggerated metabolism, but with the symptoms of the damage the latter is doing or has done to the blood-vessels. In the overfed or overworked, as previously stated, we witness the phenomena of stimulation—flushed face, brilliant eyes, with perhaps slight precordial pain after an unusually copious meal or unusual exertion, as running, climbing, etc., and general vivacity; but, it is important to note that this stage of primary exuberance corresponds with the febrile period of an infection, which may, though relatively very short, do as much damage to the blood-vessels as years of overeating, hard labor, etc. The patient, after either of these preliminary periods, long or short, passes into what is now mistaken for and described as such in most textbooks, the early manifestations of arteriosclerosis, but which are in reality those of its second stage. While in the first stage, the vessels are merely congested and more or less thickened or hypertrophied, thus causing the blood-pressure to be rather high, in this second stage organic lesions have already compromised their power to contract equably in all parts of the circulatory tree. This may affect one part of the latter more than another, or a morbid process may be awakened in one or more organs, the brain, cord, liver, kidneys, etc., according to the inherited or acquired susceptibility of these structures. Then the syndrome usually compared to neurasthenia, which is really that of a debilitated circulation, begins to appear. Loss of vigor, lassitude, or myasthenia, drowsiness, postural vertigo, faintness, more or less marked visual disturbances, phobias, headache, dyspnea on exertion, transitory hemianopsia or amaurosis—the whole gamut with which the physician is so familiar.

Here again, *prophylactic measures*, a reduction of proteins —*eliminating meats and eggs—and* any *other harmful food* the patient may be indulging in too freely are indicated. Acidosis is another feature that is harmful in these cases, which a *vegetable diet*, by supplying alkaline salts, tends to counteract and gradually to eliminate. Although the arteries are already damaged, the process of repair in them is very active, often by insular scleroses so disposed longitudinally as to restore the contractile activity of the vessels to a remarkable degree.

It is not rational to give the iodides in these cases, the thyroid secretion being already laden with iodine in organic combination and taking part in the cellular destruction of the arterial walls.

* The experience of Dr. L. Faugères Bishop coincides with mine in this particular. In fact, he refers to patients who were rendered uncomfortable by the abuse of iodides and suggests the possibility of iodism superadded to the symptoms of the disease. This is precisely what happens when the iodides are added to the thyroiodine with which the tissues are laden, the thyroid being already overactive.

The indications are precisely the opposite; no remedies should be given until the toxic factor, whatever that may be, dietetic, intestinal, bacterial, etc., is first eliminated prophylactically. If after a couple of months, the patient does not show the sense of well-being which usually follows well addressed prophylactic measures and still shows neurasthenia-like symptoms, it is because metabolism and arterial degeneration is still proceeding, owing mainly to hyperplasia of the thyroid. *Arsenic* in small doses, say 3 minims of *Fowler's solution* three times a day, as shown by Mabille and confirmed by Ewald, Heinrich Stern, and others, will then gradually reduce the thyroid erethism. In cases showing actual hyperthyroidia or larval Graves's disease, *ergotine* or the *coal tar products* are helpful to counteract the vascular supply of both the thyroid and adrenals and thus inhibit their secretory activity. It should be remembered that *rest* is an important feature wherever exuberant activity of the ductless glands is present.

The *iodides* and *digitalis*—the latter an active adrenal stimulant, a fact in which several experimenters also sustained me—are particularly *valuable late, i.e.,* when the thyroid and adrenals have been in a measure exhausted through the excessive activity that the original cause of the trouble, some toxemia, endogenous or exogenous, has imposed upon them.

Denutrition Type.—When in the form just described exhaustion of the adrenals and thyroid has occurred through the excessive activity imposed upon them by toxins, they have reached, from my viewpoint, the *denutrition type,* or the condition that prevails in what has been termed the *presenile* or *senile* form of arteriosclerosis. In some persons, even those of frugal habits, this develops early because their ductless glands through inherited debility are unable to bear the least exacerbation of activity imposed upon them occasionally by even slight intercurrent disorders, fatigue, emotions, shock, worry, *i.e.,* the wear and tear of existence. Important also in connection herewith is the influence of the diseases of children, particularly those attended by fever. Interstitial hemorrhages of both adrenals and thyroid sufficient to reduce considerably their functional efficiency cause lesions which in after life leave the organs on the very threshold of physiological activity.

Though able to carry on just the needs of commonplace existence, they prove inadequate to meet the needs of any intercurrent issue. Such people are very early the prey of intercurrent diseases, tuberculosis and pneumonia in particular. They grow old early because as the wear and tear of life impinges upon their ductless glands, denutrition progresses, including that of the arterial system. Premature involution of the thymus, as I have shown elsewhere, may initiate this denutrition type in the young.

The treatment here is the opposite of that indicated in the foregoing forms. Organotherapy, provided *thyroid* and *adrenal gland* and any other organic product used is given in small doses, is of great value. The *iodides* also in small doses, *digitalis*, and *strophanthus* are exceedingly helpful. A reduced diet here is not indicated. Besides the thyroid and adrenal preparations already mentioned, some *pancreatic product* should be added to facilitate intestinal digestion, sustain tissue life and contribute with the other organic products administered to the defensive resources of the organism.

In some cases the persistence of a high degree of arterial tension demands prompt action. An indication of this is insomnia, due to cerebral hyperæmia—a condition which, in itself, entails the danger of cerebral hæmorrhage. The sensibility of the vascular centers must then be reduced artificially. *Nitroglycerin* is the best remedy for this purpose, $^1/_{120}$ grain to $^1/_{60}$ grain (0.00054 to 0.001 gm.) being taken at bedtime and kept up a week, unless headache or nausea supervene. When it loses its effects, the other nitrites may be tried. The *bromides* or *chloral hydrate*, or better combined, giving 10 grains (0.6 gm.) on retiring, may be used as substitutes. The *bromides* alone in 20-grain (1.3 gm.) doses, as needed, are very efficacious when a high blood-pressure and headache point to the presence of considerable cerebral hyperæmia.*

J. M. Anders[76] states that sphygmographic tracings indicate the vasodilator effects of nitroglycerin in arteriosclerosis and that the drug is indicated and most effective in early cases when there is a marked increase in the arterial pressure and the heart is hypertrophied. H. J. Campbell[77] holds that when the heart is hypertrophied and its muscle beginning to fail, the main indication is undoubtedly to save the work of the heart as much as possible. The regular administration of small doses of nitroglycerin is beneficial; but massage and restricted movements are strongly contraindicated, as is also the use of digitalis, strychnine or other heart tonics. Attention to the bowels, as in all cases of cardioarterial disease, is of the first importance. The value of the bromides in such conditions I have been able to appreciate.

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* *Author's conclusion.*

[76] J. M. Anders: N. Y. Med. Jour., June 25, 1904.

When seen late, however, the hypertrophied heart may show evidences of degeneration, especially of the right ventricle. Here the judicious use of *digitalis* becomes necessary, provided the arterial tension be normal or subnormal, which is often the case when the disease is advanced. Digitalin, $^{1}/_{10}$ grain (0.0065 gm.) twice daily, is effective under these conditions. If the tension rises, *nitroglycerin, sodium nitrite or erythrol tetranitrate* may be used to counteract this effect.

The combined use of digitalis and the nitrites was introduced by Huchard and has been advocated by Balfour, DaCosta and others, but it must be resorted to with circumspection. Aged patients seldom bear digitalis well. Delancey Rochester[78] contends that it is always a dangerous drug in arteriosclerosis. Combemale[79] states that in the last stages of arteriosclerosis, digitalis and digitalin or sparteine are the only resources we have left to produce even a palliative effect.

ANGINA PECTORIS.

SYNONYMS.—*Stenocardia; Breast-pang.*

Definition.—A paroxysmal disorder of the heart the characteristic symptom of which, severe pain in and around this organ, is due to an excessive and violent influx of arterial blood into the myocardium and its nervous elements. This flooding of the cardiac muscle is due, in turn, to inability of the coronary arteries, when atheromatous, to contract sufficiently under the influence of their vasomotor nerves to prevent it when the blood-pressure of the body at large becomes high, owing to the presence, in the blood, of waste-products in sufficient quantities to excite the vasomotor center.*

Symptoms.—The most prominent symptom, pain, may be excruciating and comes on suddenly, often after mental excitement, a copious meal, exposure, a muscular effort, etc. It begins behind the sternum or in the heart, this organ feeling as if violently constricted, compressed or stabbed, and extends into the neck, the back, the shoulders, down the inner aspect of the left arm, often to the wrists and finger-tips. In some cases the pain is even more diffuse, radiating to the head and both shoulders, the trunk and lower extremities, and may be followed by anæsthesia of the left hand or arm, preceded by tingling. The face may be pale—ashen-gray rather—or flushed, and is usually covered with sweat. The features betray the intense agony to which the patient is subjected and fear of impending death. The cardiac action is often regular, but in some cases the gallop rhythm occurs or the action is turbulent and irregular, then weak and distant. The pulse varies considerably, being at one time slow and tense, then fast, and finally irregular and even imperceptible, to recover again and resume its normal action. Often, however, the pulse shows but little, if any, change. Dyspnœa, strictly speaking, is seldom present, but the respiration is shallow, a deep breath being taken at intervals. In the exceptions, however, typical asthma may be present, including the piping râles during expiration. Consciousness is seldom lost except in the final attack. In favorable cases the pain may cease as abruptly as it began, gaseous eructations and a copious flow of urine marking the end of the attack.

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[77] H. J. Campbell: Brit. Med. Jour., Oct. 12, 1901.

[78] Delancey Rochester: Med. News, Nov. 2, 1901.

[79] Combemale: *Loc. cit.*

* *Author's definition.*

In most cases, the disease begins insidiously, the attacks being at first slight and occurring at long intervals. Gradually, however, they become more severe and appear more frequently until death occurs—not always in the midst of a paroxysm, but suddenly and without warning. In other cases the attacks follow one another in rapid succession; in a third group death occurs during the first paroxysm.

Pathogenesis.—The primary cause of angina pectoris is an organic lesion of the coronary arteries. It is not, however, as now believed, due to obstruction or stenosis of these vessels, but, on the contrary, to their inability to respond to the constrictor impulses of the vasomotor nerves distributed to them, and through which the volume of blood supplied to the heart-wall is regulated.*

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* *Author's conclusion.*

As I have pointed out elsewhere,[50] the physiological rôle of the vasomotor and sympathetic network supplied to the coronaries and their branches is that fulfilled by these nerves elsewhere, viz., to constrict their muscular layer and thus reduce to its proper limits the volume of blood supplied to the heart walls. Organic changes must necessarily inhibit this function. That the coronaries are the seat of such lesions in this disease is familiar to every one. Huchard's[51] summary of 145 autopsies shows that in 68 instances there were lesions of both coronaries, and in the 128 of the total in which the presence of such lesions is specified, 121 were atheromatous. That in the remaining few, lesions capable of interfering with the nervous functions of the vessels are present, though not advanced sufficiently to be discernible, is probable. Osler[52] states that "anatomically it has been shown that lesions of the coronaries are almost invariably present."

This involves the necessity of showing that angina pectoris can occur when the coronaries are patent. Jenner,[53] for example, to whom we owe the discovery that these vessels are diseased in this disease, did not find obstruction in the cases he examined post-mortem: in the one "the coronary appeared thickened:" in the other, the vessel itself was "discovered to be a kind of firm, fleshy tube." Osler,[54] who quotes these observations, states that the coronary arteries of John Hunter, who died of angina pectoris, "were found to be converted into open bony tubes." In a case reported by Beverley Robinson[55] in which there was "terrific suffering," the coronaries, "although uniformily affected by arteriosclerosis, were of large caliber and patent throughout, except near the end of a small branch," a fact which shows that the case "was not due" to "localized sclerosis and obstruction to the lumen of the coronary arteries." Other examples of this kind are available in literature.

Conversely, the coronaries may be diseased, narrowed, obstructed and even destroyed in part without giving rise to angina pectoris. Auscher[56] found the coronaries almost occluded by atheromatous plaques, in numerous autopsies of old people who had never suffered from the disease, and he refers to Pilliet, who confirmed his observations, and found a large number of obstructed arteries which had never caused angina. Tison[57] reported two instances in which, though the coronaries were atheromatous, calcified and rigid, with great narrowing of lumen, being scarcely permeable in one case, angina had never appeared. Osler[58] refers to a case in which, although no sign of the disease had occurred, the left coronary was "almost obliterated, only a pin-point channel remaining," while the main division of the right artery "was converted into a fibroid cord."

Much confusion prevails, in my opinion, owing to erroneous interpretation of post-mortem findings. That various substances found in the non-fluid state in the tissues after death are mobile fluids during life is shown by the post-mortem formation of myosin. That the coronaries and their branches are often found obstructed by substances which during life freely circulated through them is therefore probable. This relegates to fibrosis and calcareous degeneration the main rôle as sources of obstruction, and we have just seen that they may exist without causing the disease. That life can continue even to old age notwithstanding, shows that the remaining vessels, though strained perhaps, suffice to nourish the heart-wall. It is only when, as I interpret the process, *their* walls become diseased sufficiently to respond no longer to the controlling impulses of their vasomotor sympathetic nerves, and the blood can without restraint flood the myocardium, that the anginous attacks can occur.

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[50] *Cf.* this volume, p. 1201.
[51] Huchard: *Loc. cit.*
[52] Osler: N. Y. Med. Jour., Aug. 8, 22, 29; Sept. 5, 12, 26; Nov. 7; Dec. 12, 1896.
[53] Jenner: Cited by Baron: "Life of Edward Jenner," 1827.
[54] Osler: *Loc. cit.*
[55] Beverley Robinson: Med. Record, Dec. 20, 1902.
[56] Auscher: Bull. de la Soc. anat., vol. lxvi, p. 545, 1891.
[57] Tison: *Ibid.*, vol. lxvii, p. 401, 1892.
[58] Osler: N. Y. Med. Jour., Aug. 22, 1896.

When from any cause *general* vasoconstriction occurs and the blood-pressure in the body at large is raised beyond a certain limit, an unusual volume of arterial blood—varying in each case with the degree of control to which the coronaries are still subjected—is forced into the myocardium.* The myocardial vessels being thus inordinately dilated, and the *vis a tergo* motion of the blood being unusually violent, a forceful and mechanical hyperæmia of the nervi nervorum and neurilemma of the multitude of nerves and ganglia which the heart-walls contain is caused.* This evokes the primary stage of neuritis in the cardiac structures,* and, therefore, local neuralgia.

Nothnagel, as is well known, ascribed a form of angina which he termed "Angina Pectoris Vaso-motoria" to vasomotor spasm, and the pain to the sudden increase of blood-pressure and strain imposed upon the heart. Suggestive in the present connection is his observation that the increase of vascular tension *preceded* the attack. William Russell[29] reached a similar conclusion. In the four cases reported the pulse invariably indicated the advent of an attack by becoming hypertonic; and relaxation took place when the attack ceased. In a case reported by Dodd[30] sphygmographic tracings taken by Lauder Brunton showed a high blood-pressure during the height of the attack and a lowered pressure during the inhalation of amyl nitrite, which, as first shown by Brunton, relieves the attack. These observations are confirmed by those of Fraenkel,[31] who states that, although the pulse may be but slightly or not at all affected, the blood-pressure is always raised; this author refers to Pal as having also found the blood-pressure elevated during the paroxysm. G. A. Gibson[32] ascertained that the rise was very marked, varying from 160 mm. to 170 mm. Hg.

The cardiac pain, as I interpret it in the text, is readily accounted for by the innervation of the heart-walls. Osler, referring to Berkeley's[33] histological study of the myocardium, states that "everywhere throughout the organ—in the tissue beneath the endocardium and pericardium, through the muscle substance and about the blood-vessels—the nerves are in extraordinary profusion," including *sensory* nerve-endings demonstrated in the *arteries* by Thoma and in the connective tissues by Smirnow.[34] True, as Osler says, "the most extensive lesions, inflammatory, degenerative and neoplastic, may not excite a single painful sensation. Pericarditis of the most intense grade, with deep involvement of the myocardium, may give not the slightest indication of its existence." This only proves, however, that an additional factor is necessary in this connection: that which I have shown to be the source of *neuralgic pain elsewhere*, *i.e.*, hyperæmia of the nerve-sheath itself. Indeed, Lancereaux and Peter[95] found in several cases distinct evidence of neuritis in the nerves of the cardiac plexus, a fact confirmed by Gilbert and Garnier.[96] Laënnec, Hope,[97] Trousseau[98] and other authorities regarded angina pectoris as a neuralgia.

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* *Author's conclusion.*

[29] William Russell: Brit. Med. Jour., Feb. 10, 1906.

[30] Dodd: *Ibid.*, Feb. 15, 1896.

[31] Fraenkel: Deut. med. Woch., Bd. xxxi, S. 569, 1905.

[32] G. A. Gibson: vol. xxviii, p. 52, 1905.

[33] Berkeley: Johns Hopkins Hosp. Reports, vol. iv, p. 112, 1894.

[34] Smirnow: Anat. Anzeiger, Bd. x, S. 737, 1894-95.

When the coronaries are sufficiently diseased to render the development of an attack possible, the presence in the blood of any substance capable of stimulating the vasomotor center sufficiently can provoke an attack.* Normal physiological wastes, such as those that follow the ingestion of food, suffice, in advanced cases, to cause a paroxysm, especially when the kidneys are at all diseased. In the majority of cases, however, there is a history of gout, syphilis, influenza, malaria, scurvy or other disease of a debilitating character, and which, therefore, entail, especially after middle-life, hypocatabolism and its consequences, the formation of toxic wastes and acidosis. These conditions tend not only to cause an elevation of the blood-pressure, but sudden exacerbations of the same after dietetic indiscretions, exposure, etc. Worry, grief, shock, excessive drinking, smoking, venery, etc., also prepare the ground for angina pectoris by debilitating the organism and slowing all metabolic processes.* Fits of anger and overexertion, by suddenly causing the appearance in the blood of an unusual proportion of waste-products, likewise cause a sudden rise of blood-pressure* which, in fact, may cause instant death. In some cases the general vasomotor center finally becomes oversensitive, when the least physical effort, palpation, etc., will provoke a paroxysm.

Gilbert and Garnier[99] contend that all cases of angina pectoris are of toxic origin due to uræmia. Zilgren[100] observed four cases following a febrile tonsillitis, and ascribes the disease to toxic materials derived from the tonsils. Curtin and Watson,[101] for example, observed a large number of cases after an epidemic of the last-named disease. Gélineau[102] observed many cases among sailors previously debilitated by scurvy. Excitement such as that of quarreling also provokes a rise of the blood-pressure, as shown by a case reported by Heineman.[103] Russell,[104] moreover, emphasizes the fact that in arteriosclerosis the vessels "are prone to become hypertonic from causes which are commonly regarded as trifling," and cites Pal's opinion to the same effect. Russell, moreover, states that "hypersensitiveness of the vasomotor center will explain what has long been recognized—that paroxysms of angina have as their main determining cause physical effort, mental emotion, or digestive disturbances"—a very judicious conclusion, but applicable only, as I specify in the text, to certain advanced cases. As I interpret this question, the vasomotor center is normal, as a rule, and only becomes hypersensitive when the blood contains substances which unduly stimulate it during a prolonged period.

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* *Author's conclusion.*

[95] Lancereaux and Peter: cited by Knott: Dublin Jour. of Med. Sci., May, Sept., 1897.

[96] Gilbert and Garnier: Presse méd., vol. vii, p. 263, 1900.

[97] Hope: "Treatise on Dis. of the Heart," third edition, Lond., 1839.

[98] Trousseau: "Cours de méd. clinique," Paris.

[99] Gilbert and Garnier: *Loc. cit.*

[100] Zilgren: Rev. méd de l'Est., vol. xxix, p. 612, 1897.

[101] Curtin and Watson: Inter. Med. Mag., Jan., 1893.

[102] Gélineau: Gaz. des hôpitaux, vol. xxxv, pp. 454, 466, 478, 1862.

[103] Heineman: Med. Record, Dec. 12, 1896.

[104] Russell: *Loc. cit.*

The excruciating retrosternal pain is not due to the neural hyperæmia of the myocardium, but to forcible expansion of the aorta immediately above the heart.* This portion of the vascular system is not only subjected to the stress which the resistance of the abnormally constricted arteries of the entire body imposes upon it, but also to unusually powerful contractions of the cardiac muscle, whose activity is greatly enhanced by excessive volume of arterial blood circulating through it.*

Osler[105] says in this connection: "Baumes ranked the disease as a retrosternal neuralgia (sternalgia). Laënnec gave it his strong support and held that either the pneumogastric or sympathetic division of the cardiac nerves might be implicated, and with either of them the brachial plexus." Corrigan, Romberg, Bamberger and others held the same opinion. Allbutt,[106] recalling that the most acute pain is retrosternal, above the heart and on a level with the aorta, and, moreover, that aortitis gives rise to pain which resembles that of angina pectoris, considers the aorta as the only seat of pain. That his conclusion is warranted, in so far however as to the aorta being *a* seat of pain, is suggested by the self-evident explanation of it that my conception of the morbid process, as a whole, affords.

Treatment.—MEASURES WHICH ARREST THE PAROXYSMS.—The paroxysm being due to the presence of an excess of blood in the myocardium and violent expansion of the aorta,* our aim should be to deplete these structures. *Amyl nitrite*, by causing dilation of all arterioles of the body, and, in large doses, depression of the vasomotor center besides, and therefore retrocession of the blood in the great splanchnic area, fulfills this object.* The volume of blood being reduced in the cardiac area, the myocardiac and aortic tension cease,* and the pain likewise, almost at once when a few drops of this drug are inhaled. *Nitroglycerin* acts in the same way, though not so promptly, but its effects are much more lasting, the blood-vessels remaining dilated half-an-hour or hour, or longer after an injection of

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* *Author's conclusion.*

[105] Osler: *Loc. cit.*

[106] Allbutt: Phila. Med. Jour., June 16, 23, 30, 1900.

$^1/_{100}$ grain (0.00065 gm.). This may be repeated as required to sustain the effect. When these agents cannot be readily obtained, two teaspoonfuls of *sweet spirit of nitre* in a wineglassful of water will afford relief while they are being procured.

The suffering may also be controlled with drugs capable of dulling sensibility of the heart-muscle, by causing constriction of its arterioles—including those that supply nerve elements—through their stimulating influence on the sympathetic center.[*] *Morphine*, $^1/_4$ grain (0.016 gm.) administered hypodermically, is very efficacious in this connection, when the lesions of the coronaries and its branches are not too far advanced, or the arterial tension in the cardiac area is not too great. The best results are obtained by giving it immediately after the amyl nitrite inhalations.[*] The effects of both drugs are thus insured and prolonged.[*]

This is accounted for by the fact that the drugs aid each other: amyl nitrite depletes the cardiac area, while morphine contracts the arterioles.[*] Much the same effect is produced by Waugh's method.[107] This clinician gives a granule of $^1/_{250}$ grain (0.00026 gm.) of glonoin every minute until relief ensues and the face flushes; he then deepens and prolongs the effect by giving atropine—which also contracts the arterioles[*]—$^1/_{250}$ grain (0.00026 gm.) every ten minutes till the mouth begins to become dry. It has often been noticed that morphine even in very large doses fails to produce any effect; the cause of this is self-evident when centrifugal distension of the cardiac and aortic vessels—in accord with my interpretation—is considered as the underlying cause of the pain.

MEASURES WHICH PREVENT THE PAROXYSMS.—The continuous use of morphine, belladonna, the coal-tar products and other agents which stimulate the sympathetic center is not advisable. This center rapidly weakens under prolonged stimulation and the patient's general condition is aggravated.[*] Agents which depress the vasomotor center are preferable, their benumbing effect on the latter preventing the sudden elevations of the blood-pressure which evoke the accesses.[*] *Sodium bromide*, 20 grains (1.3 gms.), alternating with *chloral hydrate*, 15 grains (1 gm.), or tincture of *veratrum viride*, 15 minims (1905 U. S. P.) (0.9 c.c.) given once daily, repeated if need be, efficiently protects the patient against attacks.[*] Nitroglycerin may be given in $^1/_{100}$ grain (0.00065 gm.) doses three times daily. *Sodium nitrite*, 2 to 5 grains (0.13 to 0.3 gm.), may be used as a substitute when nitroglycerin begins to lose its effect. *Erythrol tetranitrate* in 1-grain (0.065 gm.) doses four times daily has been highly recommended. All these agents are vasomotor depressants.

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[*] *Author's conclusion.*

[107] Waugh: Therap. Gaz., Nov. 15, 1902.

Nitroglycerin is a useful agent in this connection. William Murrell[108] states that the best results are obtained when the spirits of glonoin are used. His preferred formula is:—

℞ Spiritus Glonoini (B. P.),
Spiritus Chloroformi, aa, $^{1}/_{2}$ drachm (2 gms.).
Tinct. Capsici, 1 drachm (4 gms.).
Aq. menth. pip., ad 1 ounce (30 gm.).

A teaspoonful every four hours, an extra dose being taken immediately on the onset of the attack.

He advises that this be a stock bottle from which should be replenished three or four small bottles containing a drachm each, which can be carried in the vest-pocket for immediate use when needed. Erythrol tetranitrate has been recommended by J. B. Bradbury,[109] Adam,[110] Boughton Addy[111] and others. Huchard[112] deems it capable of maintaining continuously the vascular tension close to its physiological limits.

The attacks may be reduced and even prevented by *dietetic measures*, the most important of which is to limit the amount of food taken and to abstain from the use of meat, the catabolic products of which are especially active as vasomotor stimulants.* Late suppers are particularly harmful, and even dangerous. A *milk diet* of two weeks' duration, aided by one of the nitrites, is very efficacious, even in severe cases. The limited diet is sufficient in some instances to avert paroxysms, provided worry, violent exertion, and other exciting causes can be avoided.

Huchard[113] states that angina with endocarditis is relieved by an exclusive milk diet and theobromin for two weeks, then one week each month with sodium iodide. During the rest of the month a restricted diet is allowed. Osler regards the diet in many cases as "the central point in the treatment." Russell emphasizes the close relationship between an injudicious diet and a high vascular tension and adduces cases proving this contention.

The progress of the disease may often be stayed by the use of *potassium or sodium iodide*, 5 grains (0.3 gm.), gradually increased to 10 grains (0.6 gm.) after meals, after the patient has been on the restricted diet two or three weeks. *Thyroid gland*, 1 grain (0.06 gm.) three times daily, is also useful.*

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* *Author's conclusion.*

[108] William Murrell: Med. Brief, May, 1897.

[109] J. B. Bradbury: Brit. Med. Jour., Apr. 10, 1897.

[110] Adam: *Ibid.*, Feb. 12, 1898.

[111] Boughton Addy: *Ibid.*, May 6, 1899.

[112] Huchard: Revue de thérap. méd.-chir., vol. lxx, p. 428, 1903.

[113] Huchard: Jour. des praticiens, Feb. 23, 1901.

By stimulating the adrenal center, catabolism is enhanced and toxic wastes do not form. The nutrition of the arteries being gradually improved, the primary morbid process, arterial degeneration, is antagonized. An important feature of the treatment is to avoid constipation and intestinal autointoxication. An occasional *saline purgative* suffices for this purpose.

Strychnine and *digitalis* are casually mentioned by some authors. Strychnine, being a vasomotor excitant, predisposes to attacks, while digitalis by enhancing the vigor of the heart's contractions may aggravate the attacks—a fact sustained by clinical observation. I regard these drugs as harmful as long as paroxysms are likely to occur.

CEREBRAL HÆMORRHAGE.

SYNONYMS.—*Apoplexy; Cerebral Apoplexy.*

Definition.—An effusion of blood in the brain due, in the majority of (idiopathic) cases, to rupture of an atheromatous artery, and the exciting cause of which is an unusually high blood-pressure. The pathogenesis is that of arteriosclerosis, including the rôle of the adrenal system in this disease.*

Symptoms.—*Prodromal symptoms* occasionally occur: headache or a sensation of fullness in the head, vertigo, tinnitus, excitability, abnormal sensations on one side of the body, especially the extremities, such as tingling, numbness and choreic movements.

The *apoplectic stroke* itself may be preceded by slight vertigo, slight aphasia and unilateral weakness, and paralysis of a leg or arm; but often without any such symptoms the patient drops suddenly, and, occasionally, after a few convulsive movements, becomes comatose. The face is dusky and even cyanotic, though sometimes pale, the pulse slow and relatively strong, full and tense; the breathing slow and stertorous, and often of the Cheyne-Stokes type, the cheeks being blown out on one side and the lips being flabby, owing to paralysis of the muscles of these structures. In ingravescent apoplexy the symptoms come on gradually, in keeping with the slow progress of the effusion.

In some—usually very severe—cases the face becomes very

**Author's definition.*

pale or livid, the pulse and heart beat feebly, all muscles relax, and the patient may die after being comatose a short time, or he may remain unconscious some time, recover somewhat, and die in the midst of a second seizure; or again, he may improve and follow the course of a less severe case.

The peripheral effects of the cerebral lesion then become manifest, one side of the body, including the facial and ocular muscles (the eyes being turned toward the side of the lesion), being as though paralyzed. The cutaneous reflexes may be elicited by vigorous stimulation, pinching, pricking, etc., but, as a rule, all the reflexes are abolished at first on the affected side, and often on the normal side as well. The pupils are often unequal in size, contracted at times and dilated at others, and respond slowly or not at all to light. The feces and urine are usually passed involuntarily. There is often polyuria, the urine often containing sugar and albumin.

The period of *reaction* is initiated by fever, the temperature, one or two degrees F. below normal after the onset of attack, now rising to 101° F. (38.3° C.), or even to 103° F. (39.4° C.). After a period varying from a few hours to several days, the patient recovers from the coma, more or less dazed, restless or even delirious, especially if the fever is marked.

The paralyzed muscles may now become temporarily rigid and even spastic, but ultimately the loss of power again becomes manifest, affecting all the muscles of one side, though differences in degree of paralysis exist between the arm and leg, or between the face and extremities,—the leg escaping, for instance, while both the face and arm are paralyzed, etc. The cheek and lips of the corresponding side remain relaxed, as they were during the comatose period; the tongue, when protruded, is pointed toward the paralyzed side, and the loss of function of one-half of its muscles causes speech to be thick and almost unintelligible. The sphincter muscles may preserve their activity, however, at least for a time, and the reflexes, abolished at first on both sides, may now return, and also, after some time, on the paralyzed side, where they ultimately become exaggerated, though the electric reactions show no change.

The period of *resolution* begins when the paralytic phenomena show improvement, especially in the muscles of the leg.

As it is the extensors which recover their contractility, the limb remains stiff, and when the patient is able to walk, the leg is swung around in a semicircle at each step, the toes scraping the ground. This gives the patient the characteristic gait. It is regarded as an unfavorable omen when the arm is the first to improve. What improvement occurs in this extremity is in the flexors and pronators, the arm being thus drawn close to the body with the wrist flexed, the forearm semi-pronated and the fingers closed over the flexed thumb.

An important feature of this stage is that passive motion is readily performed. The paralyzed muscles are structurally normal, but being of the voluntary type they are not used and, failing to be nourished, become rigid, tend to contract and to remain fixed in this condition—the "contractures" so commonly observed in this disease. When this has occurred passive motion is no longer possible. Symptoms due to impaired nutrition are often discernible in other structures, the skin of the arms, for example, which may become red and lustrous and cold. The readiness with which extensive sloughing occurs on the paralyzed side in bed-ridden patients also points to impairment of the nutritional functions. Complete paralysis, even of the arm, does not always occur, however; after a few months in some cases, the use of the fingers, hand, forearm and arm is gradually and progressively regained.

The term "resolution" I apply to this period seems irrelevant when the frequency with which paralysis follows a stroke of cerebral hæmorrhage is taken into account. Yet, in the light of my views, as will be shown under "Treatment," such an untoward result is probably avoidable, and such being the case, "resolution" becomes applicable.

The symptomatology of the stroke itself varies considerably as to intensity in different cases, and the ultimate result corresponds, in a measure, with the severity of the primary phenomena. Among the *favorable signs* are: a brief duration of the coma; motion, even though slight, of the paralyzed limb during the first twenty-four hours; a moderate rise of temperature when reaction occurs (102° F., 38.9° C.), and restricted paralysis, brachi-crural, facio-brachial, etc. The *unfavorable signs* are: prolongation of the coma beyond twenty-four hours; marked hypothermia; initial convulsions; profuse sweating; cyanosis; conjugate deviation of the eyes; a steady rise of the *temperature to 104° or 105° F. (40° or 40.5° C.)* when reaction occurs, with marked intensification of the knee-jerk and bilateral paralysis.

William Browning[114] states that in children the chances of partial recovery are good; that in adults the recovery depends upon the severity of the apoplectic attack; and that in old age, when the arteries are tortuous or calcified, but limited recovery is to be expected. Barrs[115] concludes that if either renal disease, Cheyne-Stokes respiration or hyperpyrexia be present, the patient will probably not recover.

Pathogenesis and Pathology.—Whether we ascribe the rupture of the artery to miliary aneurisms, to endarteritis, to the so-called "fatty erosion" or to "diffuse degeneration," we are always brought back in cerebral hæmorrhages that are not due to traumatism or to an acute infection, leukæmia, etc., to a common cause: arteriosclerosis, the lesions being similar to those of that disease (*q.v.*). The multiple causes of arteriosclerosis: overeating (gout), alcohol, syphilis, senility, excessive exertion, excitement, starvation, lead, etc., are likewise those of arteriosclerosis. This applies as well to the renal lesions of this disease. On the whole, the relations of cerebral hæmorrhage to the adrenal system are those of the latter to arteriosclerosis.*

The reader is referred to the article on Arteriosclerosis for the details of the process. Whittaker[116] writes in this connection: "In all cases the process depends upon arteriosclerosis, which runs a slow and insidious course for months and years, and usually eludes all discovery. The catastrophe is sudden, but the disease process which leads up to it is very slow." Allen Starr,[117] in a study of 200 cases of apoplexy, found that 80 per cent. presented prodromal symptoms which he regarded as probably due to arteriosclerosis. Broadbent,[118] in a study of the vascular changes in 16 cases, found senile degeneration of the vessels in 2, while 7 were associated with granular kidney, and 7 with a type of kidney in which the main changes were thickening and hyaline degeneration of the vascular intima. The cerebral vessels were *dilated*, thinned and hyaline or studded with white patches, which, on microscopic examination, were found to consist of localized thickening and degeneration of the subendothelial tissues, over which the muscular coat, thin and atrophied in some instances, could not, as a rule, be traced. These are, we have seen, precisely the lesions found in the arteries of the body at large in arteriosclerosis. Stein[119] observed the typical loss of elasticity, and states that miliary aneurisms are far less frequent than is generally believed, the lesion being atheromatous.

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* *Author's conclusion.*

[114] William Browning: Sajous's "Analyt. Cyclo. of Pract. Med." vol. ii, p. 127, 1898.

[115] Barrs: Brit. Med. Jour., May 18, 1895.

[116] Whittaker: Indiana Med. Jour., May, 1896.

[117] Allen Starr: Med. Record, July 4, 1903.

[118] Broadbent: Lancet, Feb. 20, 1904.

[119] Stein: Deut. Zeit. f. Nerv., Bd. vii, S. 312, 1895.

Unfortunately the phenomena which make it possible to recognize the presence of arteriosclerosis, hardening of the radial and temporal arteries, the arcus senilis, etc., are not always present. The arterial lesion being present, coughing, sneezing, straining, etc., may suddenly increase the general vascular tension and cause rupture of the vessel, a mass of blood varying in size from that of a small cherry to that of an orange or more being suddenly projected under a pressure varying from 100 to 200 mm. Hg. upon the brain. As it coagulates at once, it forms a relatively dense body which may forcibly compress or disintegrate more or less the brain-substance, and as this substance is not renewed in the latter case, permanent lesions remain. The "stroke" is the result of shock, which reacts upon the entire cerebrospinal system, while the loss of consciousness is due to the suddenly-induced cerebral anæmia.

The hæmorrhage is derived either from a meningeal or central artery, but rupture of a meningeal branch is often due to traumatism. In most cases it occurs within the field of the central branches of the circle of Willis rather than in the cortical branches of this circle. The branches of the middle cerebral artery, which penetrates the brain by way of the anterior perforated space, are especially prone to rupture; this applies particularly to a branch that passes to the internal capsule and the lenticular nucleus and which has been named by Charcot the artery of "cerebral hæmorrhage."

Though any portion of the brain may become the seat of the hæmorrhage, certain regions suffer more frequently than others. The principal among these are, in the order of diminishing frequency: the internal capsule, the corpora striata, the thalami optici, the corona radiata, the convolutions and the pons Varolii.

The pressure in the central vessels is very great, owing to their proximity to the great channels, the carotids. Hence the predisposing influence of a short neck, especially in massive, full-blooded individuals. Stein[120] showed that the pressure of the blood projected into the cerebral tissues was 100 to 200 mm. Hg. The destructive action becomes obvious in view of the fact that the same tissues under normal conditions are subjected to a pressure of only 10 mm. Hg. Boudet[121] reported a case in which three-fourths of the right hemisphere was destroyed. Norbury[122] emphasized the importance of the great pressure in the basilar arteries as well as in the median cerebral arteries and the thinness of the walls of the cerebral vessels which predispose them, when they are the seat of atheromatous or miliary aneurisms, to hæmorrhage. Zapinsky[123] in 15 autopsies found degenerative lesions in the vessels of the base in every instance, the atheromatous plates being sufficiently marked to be seen with the naked eye.

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[120] Stein: *Loc. cit.*

[121] Boudet: Cited by Whittaker: *Loc. cit.*

[122] Norbury: Medicine, July, 1897.

Treatment.—Measures to Prevent the Development of an Attack.—In some cases some of the prodromal symptoms, slight thickness of speech, torpor, or numbness of an extremity, headache, vertigo, fullness in the head, etc., occur several days before an attack. When there is any evidence or likelihood of arteriosclerosis, measures should at once be instituted to prevent the stroke. If the arterial tension is high, the pulse tense and hard, an attack may occur at any moment; agents which cause immediate relaxation of the vessels by obtunding directly the vasomotor centers* are necessary. Among these are *nitroglycerin,* which acts on the pulse in two minutes, and the effects of which have entirely passed off in three hours; *sodium nitrite,* the action of which shows itself in about five minutes and lasts the same length of time; *erythrol tetranitrate,* in the solid form, acts in from twenty to thirty minutes, and its effects continue from seven to eight hours. To thwart the attack, therefore, either of the two first agents should be given every two hours and the third every six hours. An immediate result may be obtained with *amyl nitrite,* 5 drops, inhaled from a handkerchief; or a slight degree of help may be derived from *sweet spirits of niter,* two teaspoonfuls in a little water, pending the arrival of a stronger vasodilator.

The period of onset and the duration of the effects of nitroglycerin are those given by C. R. Marshall,[124] those of sodium nitrite by Leech,[125] and those of erythrol trinitrate by Bradbury,[126] both cited by Marshall.

Important in this connection is the avoidance of any effort or excitement and of agents which tend to stimulate the patient and cause a rise of the blood-pressure: stimulants, emetics, digitalis and strychnine are particularly harmful in this connection. Strophanthus and potassium iodide, casually mentioned by some authors among the useful drugs, are also contraindicated in threatened apoplexy. Saline injections may also prove harmful by increasing the body fluids and the blood-pressure. The bowels should be kept free, to avoid autointoxication.

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* *Author's conclusion.*

[123] Zapinsky: Wratch, No. 4, p. 95, 1896.

[124] O. R. Marshall: Brit. Med. Jour., Dec. 11, 1897.

[125] Leech: *Ibid.,* July 1, 1893.

[126] Bradbury: *Ibid.,* Nov. 16, 1895.

As attacks sometimes come on at night owing to the recumbent position, vasomotor depressants should be taken on retiring. To those mentioned may be added *sodium or potassium bromide, chloral hydrate* and *veratrum viride*. These three agents may be advantageously combined.

The patient's diet should be light, and coffee, tea, and other stimulating beverages should be dispensed with.

Preston[127] rightly holds that more could be done in the prodromal stage if this condition were carefully studied.

MEASURES TO PREVENT EXTENSION OF THE CEREBRAL LESIONS DURING THE ATTACK.—After the first outpour of blood, the hæmorrhage almost always continues some time, and if steps be taken to decrease the cerebral blood-supply, the extension of the lesions may be, to a certain extent, curtailed, provided the patient be seen sufficiently early.

The patient is usually found lying on his back; his trunk and head should be gently raised until he is in a semirecumbent posture; the back and head being supported by the back of an overturned chair, made comfortable with pillows if these are available. If the face is dusky or cyanotic and the pulse is hard, incompressible, inhalations of *amyl nitrite*, 6 to 8 drops or more, should be resorted to, the handkerchief upon which the drug is poured being held in front of the patient's mouth and nose. This causes immediate relaxation of all arteries and the patient is bled, as it were, into the large trunks of the splanchnic area. In the meantime, the necessary preparations for *venesection* having been made, the patient should be bled. The brain is thus relieved instantly by the drug, and kept in that condition by the bleeding; the destructive process is thus necessarily counteracted. To prevent recurrence of the high vascular tension *veratrum viride*, 10 drops or more, if need be, of the tincture (1905 U. S. P.), should be given every two hours.

Browning[128] writes in this connection: "Some cases are promptly fatal, meningeal and ventricular forms being usually of this kind. Nearly always, however, the effusion progresses for some time. It is here that the physician can be of great service." Some clinicians having advocated the recumbent position, Heidenhain[129] refers to several instances in which the placing of this position had been followed immediately by aggravation. Osler, Tyson, Bramwell[130] and others all recommend venesection, the latter stating that it is contraindicated when the pulse is feeble, rapid or irregular, the heart dilated and weak, and the patient very old and debilitated. As illustrated by a case reported by Benham,[131] it tends furthermore to arrest convulsions, which, owing to the intense vascular tension accompanying them, must increase greatly the cerebral effusion. The value of the measures outlined above are further suggested by the fact emphasized by Grasset[132] that "whatever may be the pathogenic theory regarding apoplexy, it is essentially characterized by a congestive condition of the head and by circulatory erethism."

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[127] Preston: Maryland Med. Jour., July 29, 1903.

[128] Browning: *Loc. cit.*

[129] Heidenhain: Berl. klin. Woch., Bd. xxvii, S. 126, 1890.

A purgative aids the remedial process by further depleting the vascular system. By causing, moreover, congestion of the intestinal vessels, it acts as a derivative besides insuring the elimination of substances capable of causing autointoxication: Two drop[illegible]*oton oil* mixed with a little glycerin or olive oil, dropped on the back of the tongue, or 1/4 grain (0.016 gm.) of *elaterium* dissolved in a little water in the same manner are usually employed with advantage. An *enema* of lukewarm water is also useful. A hot *foot-bath* also serves a good purpose as a derivative.

By this time the patient has received all the truly useful attention he requires. Counterirritation to the neck serves only to irritate him by increasing his discomfort. The ice-bag placed on his head to meet the popular notion on the subject only serves to contract the peripheral vessels and increase in proportion the internal pressure—while affording a second source of discomfort.

As in the premonitory stage, all stimulants and tonics, including particularly strychnine, digitalis and the iodides, should be avoided, as they all tend to raise the blood-pressure.

It is often necessary to relieve the bladder by means of the catheter.

MEASURES TO AID THE PROCESS OF RESOLUTION.—When the *reaction* sets in, the fever is a protective phenomenon—an effort of the organism to rid the brain of the hæmorrhagic coagulum and of what detritus has accumulated around it. *Trephining* has been used with success to remove a meningeal clot, but a clot in the deeper tissues is usually beyond reach. *Potassium iodide* is usually given at this stage in the hope of hastening the absorption of the clot, but, like digitalis, it increases the vascular tension in the usual therapeutic doses, and, therefore, exposes the patient to another stroke. It is preferable to allow the physiological resources of the body to act without interference on our part.*

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[130] Bramwell: Treatment, July, 1897.
[131] Benham: Brit. Med. Jour., Mar. 21, 1896.
[132] Grasset: Méd. moderne, vol. ix, p. 1, 1898.

Whittaker[illegible] writes in this connection: "Certain lymph cells, phagocytes, begin at once to remove the obstruction, and cells which incorporate blood-corpuscles are seen as early as the third day. Dürck found on the eighteenth day free pigment, and nothing but pigment on the sixteenth day."

When the period of *resolution* has set in, however, much may be done to prevent the development of paralysis.

We have seen that the cerebral lesions are located in the brain proper, the source, therefore, of voluntary impulses, the spinal system *per se*, governed by the pituitary body and the source of involuntary, *i.e.*, automatic impulses, remaining whole.* The loss of voluntary stimuli does not mean, however, that the spinal system has lost its control over the muscles of the paralyzed side, or that the vasomotor supply through which the muscles are nourished is the least impaired.* It only means that the strictodilator nerves which incite function in certain muscles no longer receive *one* of the two kinds of stimuli which they are in the habit of receiving through the intermediary of the cord, *i.e.*, the *voluntary* from the impaired area of the organ of mind, in contradistinction to the *automatic* from the somatic brain, the pituitary body.* Even this may be reduced to a mere question of quantity as far as the vasa vasorum (which, when constricted, cause the arterioles they nourish to dilate and admit more blood into the muscular elements) are concerned, since all impulses to them, whether originally derived from the brain or from the spinal cord, serve but one purpose, namely, to provoke their constriction.*

Such being the case, paralysis finally occurs, merely because the muscles are *allowed* to degenerate through deficient use.* It would be prevented to a great extent, and perhaps altogether in some cases, were measures to do so initiated as soon as the patient has recovered from the immediate effects of the paralytic stroke.

The reader is referred to the sixteenth chapter for evidence to the effect that all somatic functions, including intricate muscular movements, can be performed independently of the brain. Not only do extensive injuries of the hemispheres—the crow-bar case, for instance—fail to impair muscular activity, but even their entire removal as in so high a mammal as the dog, will fail to do so. This has been shown by Goltz's animal, which lived eighteen months after both lobes and a part of the optic thalami had been removed. That timely measures are useful is shown by the following lines of Browning's:[104] "Recently a German writer has done good service by calling attention to the importance, in these cases, of doing everything to bring activity again into the patient's nerve tracts. He shows that by rousing these persons, lifting them—when not too feeble—into a sitting position, getting them once more interested in life; further by *exercising actively* and *semi-passively* the *paretic muscles*, we can save the patient from *further degeneration* that so often ensues and may effect great gain. To the value of this principle I can heartily subscribe. Ere beginning this plan, however, we must wait until the danger of immediate relapse is past—say, usually until the end of the first week or ten days." The practical side of the question thus sustains the explanation I submit.

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* *Author's conclusion.*

[illegible] Whittaker: *Loc. cit.*

An important practical point in this connection is that the vitality of muscles can be preserved reflexly, and enhanced when defective, by massage. The latter should be begun as soon as possible, therefore, avoiding much pressure. The muscles of the trunk, especially the trapezius, should not be overlooked in this connection. Passive movements should follow the massage, taking care to give each member exercise in the line of its usual functions. Thus, the fingers should be gently flexed and unflexed upon the hand, and separated and approximated; the arm likewise at each joint, and rotated, etc. After the massage and passive motion, the patient should attempt to repeat the same motions voluntarily. He will be aided in this not only by the temporary increase of nutrition which the previous procedures will have brought about, but also by the fact that the *somatic* brain is able to supply, when movements are alone in order, impulses which strikingly recall those projected by the organ of mind.*

Interpreted from my standpoint, manipulations such as those practiced by osteopaths and masseurs promote nutrition of the structures thus treated by enhancing reflexly the propulsive activity of the arterioles through the sympathetic, and aid materially thereby the restoration of function.

When the patient is able to go about, he should be treated as a case of arteriosclerosis—a condition quite amenable to treatment in a large proportion of cases.

Many highly accomplished men, including Samuel Johnson, have lived many years of usefulness after an attack of apoplexy. As to disability, Whittaker refers to the fact that Schmidt "described 39 cases of cerebral lesion in which no sign of brain affection could be demonstrated during life," these cases constituting one-third of all of local lesions which came to autopsy during eight years in Eichhorst's clinic.

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* *Author's conclusion.*

[104] Browning: *Loc. cit.*

DIABETES MELLITUS.

SYNONYM.—*Glycosuria.*

Definition.—There are two forms of glycosuria: (1) *Diabetes Mellitus,* due to hyperactivity of the adrenal system, and (2) *Asthenic Glycosuria,* due to hypoactivity of the adrenal system.*

Diabetes mellitus, an excessive excretion of sugar and urine, is due to hypersensitiveness of the test-organ, and to the presence in the blood of waste-products or other irritating substances which keep this organ, and through it the adrenals, overactive. An excess of adrenoxidase is thus produced, and the intrinsic metabolism of all tissues is correspondingly activated. The pancreas being thus caused to secrete, besides its other ferments, an excess of amylopsin, the hepatic and muscular glycogens are converted into sugar with unusual rapidity, and the surplus of sugar formed is eliminated by the kidneys.*

Symptoms.—The onset of diabetes mellitus is insidious, and any one of its symptoms may appear first. As a rule, however, the earliest phenomena observed are unusual thirst and dryness of the mouth and pharynx, and viscidity of the saliva. Polyuria may either appear concurrently or be the first symptom observed, the excretion of urine being increased to a daily quantity varying from 6 to 30 pints or more, the urine itself being pale and acid, and having a specific gravity varying from 1020 to 1040, or even higher. It contains from $^1/_2$ to 5 per cent. or more of sugar (glucose), the daily excretion of which may vary from one ounce to as much as two pounds. Stains on the linen or on the shoes or clothing, where drops of urine happen to fall, prove on analysis to be sugar.

The patient may sweat profusely under the influence of slight exertion or during moderately warm weather, or his skin may be dry or more or less harsh owing to deficient perspiration. Pruritus may cause considerable suffering, especially in women, owing to involvement of the meatus urinarius and the labia.

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*Author's definition.

The gums may become spongy and the teeth show an unusual proclivity to caries; recession of the gums is also apt to occur in these cases and render the teeth liable to fall out. The tongue is often red, dry and glazed; the breath may have a peculiar odor recalling that of apples. Excessive appetite is a common symptom, though the patient gain no weight or even lose flesh and grow weaker.

These symptoms may appear in rapid succession and the case remain a benign one—at least for a time—or they may develop very slowly, constituting a chronic case.

As the disease progresses, *complications* may occur. Neuritis, especially of the brachial and crural nerves, is frequently observed. Gangrene may be readily produced by what under normal conditions would prove to be trifling injury or disorder, an abrasion, a boil, etc.; it is apt to begin in an extremity, especially the toes, and to extend upward. Gastrointestinal disorders are frequently observed, consisting of indigestion with pyrosis and gastralgia, constipation and flatulence, or diarrhœa. The odor of the breath changes to an unpleasant one, suggesting that of vinegar or stale beer. The patient at this stage is especially prone to intercurrent diseases, especially those of the respiratory tract, tuberculosis, pneumonia, bronchitis, etc. Carbuncles are frequently observed in the course of the disease and promptly assume an alarming aspect.

In *advanced cases* the temperature, though not materially affected early in the disease, may become subnormal. The tendon reflexes are, as a rule, diminished. Symptoms recalling those of tabes, the so-called "diabetic tabes," may occur, with "steppage" gait and paralysis of the extensors. Atrophy of the optic nerve, cataract and other disorders of vision may appear, both eyes being affected simultaneously. The other organs of special sense may likewise become impaired. Impotence, sterility and abortion are common complications, as is also interstitial nephritis.

Diabetic coma occurs in advanced cases, usually as a fatal complication. It is often preceded by general malaise, irritability, vertigo, anxiety, constipation with abdominal and muscular cramps. Conversely, it may occur suddenly with special premonitory symptoms, the patient lapsing into unconsciousness, with the eyes half closed, the respiration sighing, the pulse rapid and weak. The temperature, at first somewhat above normal, gradually declines, cyanosis appears, the precursor of death, which ensues usually between twenty-four and forty-eight hours after the onset of the coma. Death from coma occurs, however, in less than half of the cases of diabetes.

Diabetes mellitus, as here understood, begins in sthenic and more or less vigorous subjects.*

Pathogenesis and Pathology.—Diabetes mellitus is due to excessive irritability of the test-organ and to the presence in the blood of waste-products, stimulating drugs, poisons, toxins, etc., which cause this organ to react inordinately owing to its over-sensitive condition. By thus provoking an excessive production of adrenal secretion, these agents excite hyperoxygenation of all organs, including the pancreas.* As this organ (its islands of Langerhans) supplies a ferment, amylopsin, which on reaching the muscles through the intermediary of the leucocytes,* and the liver by way of the splenic vein,* converts the glycogen of all these organs into sugar, a larger quantity of the latter is produced than usual, and the excess is promptly excreted by the kidneys.* Hence the presence of a more or less great quantity of sugar in the urine, the excess voided over and above the normal ratio being proportionate with the degree of hyperactivity of the adrenal system.*

In the first volume of this work (Jan., 1903)[125] I concluded, after submitting evidence to that effect, that toxic glycosuria was "primarily due to overstimulation of the adrenal system, the excessive functional activity which increased oxidation produces giving rise to an inordinate production of an agency that converts glycogen into sugar." In the present volume[126] I pointed out that diseases of the anterior lobe of the pituitary body (the seat of the adrenal center) attended by hyperæmia or hypernutrition provoked glycosuria, and that the adrenal center was the so-called "glycogenic center." This term applies, interpreted from my standpoint, only in connection with the *abnormal* production of sugar, for I regard the vagus center as the true "glycogenic center" in the sense that it adjusts the conversion of glycogen to the physiological needs of the body at large, by regulating simultaneously the functions of the pancreas and the liver. The production of glycosuria by stimulation of the adrenal center accounts (1) for the fact that Blum, Herter, Croftan and others produced this symptom by injecting adrenal extract; (2) for the cessation of toxic glycosuria when, as observed by Claude Bernard, Kauffmann and others, the splanchnics—which contain the nerves from the adrenal center to the adrenals—were severed; (3) for the recent observation of André Mayer[137] that after extirpation of the adrenals Claude Bernard's puncture no longer provoked glycosuria; and (4) for the rapid diminution of sugar both in normal glycæmia and glycosuria, when, as observed by Kauffmann, the inferior vena cava—to which the adrenal secretion is carried by the adrenal veins—was ligated. As all these observations had remained unexplained before I had shown the functional relationship between the pituitary body and the adrenals, they now stand as evidence of the correctness of my interpretation.

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* *Author's conclusion.*

[125] *Cf.* vol. i, p. 386

[126] *Cf.* this vol., p. 1021.

As the adrenal system includes the thyroid gland, thyroid extract should also cause glycosuria. This fact was not only observed by Ewald in 1894 and by many observers since, as we have seen in the seventeenth chapter and as shown below, but Lorand found that it was even more active than adrenal extract in this particular.

The "internal secretion" referred to in the text only means, according to the current view, the substance secreted by the islands of Langerhans as distinguished from the pancreatic juice secreted externally, *i.e.*, in the intestinal canal. The manner in which this substance reaches the liver, however, has not been shown. In the first volume[138] I suggested that the sugar-forming ferment passed out of the pancreas with its venous blood *into the splenic vein;* that it met in the latter the internal secretion (nucleo-proteid derived from broken-down leucocytes) of the spleen, which rendered it active, and then passed to the portal system, where it converted glycogen into sugar. Additional evidence to this effect is available in the literature on the pathogenesis of glycosuria; a small part of which only can be submitted here.

We owe to Mering and Minkowski[139] the view that the pancreas produces an internal secretion which governs carbohydrate metabolism and to Laguesse[140] the demonstration that the islands of Langerhans were the source of this secretion—both of which conclusions have been repeatedly sustained, especially by Schäfer's[141] independent researches. But Laguesse[142] concluded, moreover, that the secretion-granules of the islands, at least in the embryo, were carried away by the blood-vessels. This applies to the developed islands as well, since they also are deprived of ducts. My own conclusion that it is carried to the splenic vein not only affords the only normal path for the internal secretion to the liver, but it explains also why ligation of the pancreatic duct, while causing disuse-atrophy of the rest of the pancreatic parenchyma, leaves the islands of Langerhans practically unharmed, thus showing that their functions are not arrested. Indeed, as shown by Ssobolew[143] in the guinea-pig, rabbit, cat and dog, the islands persisted 400 days, *i.e.*, until all the vital activity of the glands had ceased. Moreover, the atrophy of the gland elements did not modify carbohydrate metabolism; it only became impaired when the entire gland, including therefore the islands of Langerhans, had been extirpated.

Conversely, Arthaud and Butte[144] arrested glycosuria by ligating the veins of the pancreas, which open, as is well known, into the mesenteric and splenic veins. This result (although the observers mentioned in no way refer to the possibility of an internal secretion such as that suggested by myself twelve years later) proves conclusively that it is through its veins that the internal secretion which provokes glycosuria enters the circulation and through it the liver.

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[137] André Mayer: Arch. gén. de méd., July 17, 1908.
[138] *Cf.* vol. i, pp. 367 *et seq.*
[139] Mering and Minkowski: Arch. f. exp. Pathol., Bd. xxvi, S. 371, 1890.
[140] Laguesse: C. r. de la Soc. de biol., 9 série, vol. v, p. 819, 1893.
[141] Schäfer: Lancet, Aug. 10, 1895.
[142] Laguesse: *Loc. cit.*
[143] Ssobolew: Virchow's Archiv, Bd. clxviii, S. 91, 1902.
[144] Arthaud and Butte: C. r. de la Soc. de biol., 9 série, vol. ii, p. 59, 1890.

As to the participation of a splenic internal secretion in the glycogenic process, I must refer the reader to the first volume[145] for details, in which its action upon trypsinogen is studied, and which applies to the carbohydrates as well. Referring to the investigators and the researches I mention therein, Hammarsten[146] says: "Such a 'charging' of the pancreas by the spleen has been repeatedly suggested by Schiff, and his statements have not only been confirmed by these recent investigations, but in part also explained." He also states, however, that this is caused "in a still unknown manner by a body whose nature is unknown."

We thus have for the conversion of glycogen into sugar a triad composed of the blood's adrenoxidase and nucleo-proteid from the spleen which, by their interaction, supply the heat-energy required to activate the pancreatic proferment amylopsinogen, to which the conversion is due, the three forming, in reality, the compound* now known as amylopsin.

Several drugs in common use are capable, in sufficiently large doses, of provoking glycosuria: adrenal extract, which causes it indirectly by enhancing the oxygenation of the pancreas; thyroid extract, which initiates the same process by stimulating the adrenal center; strychnine, mercury and other drugs, which also stimulate the adrenal center, but less vigorously.*

Various diseases, the pathogenic agents of which cause marked stimulation of the adrenal center,* may also provoke glycosuria. These include pertussis, measles, varicella, diphtheria, enteric fever, epilepsy, convulsions and malaria, and diseases such as gout and rheumatism, but only during exacerbations of adrenal activity caused by an accumulation of toxic wastes in the blood.

We have seen that adrenal extract readily provokes glycosuria. Thyroid extract, which acts much as does the thyroid secretion itself, by stimulating the adrenal center, was found to produce marked glycosuria by W. Dale James[147] in the case of a physician who had taken thyroid for a psoriasis of old standing. The sugar disappeared when the use of the drug was discontinued. Similar cases have been observed by Ewald,[148] Lorand and other clinicians. Georgiewsky[149] found that in dogs the use of fresh thyroid gland as food, or of the expressed juice by injection, produced a glycosuria which sometimes reached as much as 17 per cent., and which disappeared when the thyroid was no longer given. Strychnine was found to cause glycosuria by Claude Bernard, Schiff and many others; Demant[150] showed that it caused the hepatic glycogen to be rapidly reduced. Langendorff[151] observed, moreover, that extirpation of the liver prevented strychnine glycosuria. The clinical use of mercury was also found to bring on glycosuria by Reynoso, Rosenbach, Bouchard and others. Handfield Jones[132] noted, moreover, that mercury caused marked hepatic hyperæmia. Phloridzin glycosuria is likewise due to marked stimulation of the adrenal center. The fact that it is accompanied by excessive metabolism is shown by Cartier's[133] statement that "all authors who have studied phloridzin unite in saying that the animal experimented upon becomes voracious, and, if not overfed, rapidly wastes."

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* *Author's conclusion.*

[145] *Cf.* vol. i, pp. 367 *et seq.*

[146] Hammarsten: "T. B. of Physiol.," p. 323, 1904.

[147] W. Dale James: Brit. Jour. of Dermat., June, 1894.

[148] Ewald: Deut. medizinal Zeitung, S. 669, 1894.

[149] Georgiewsky: Centralbl. f. d. med. Wissen., Bd. xxxiii, S. 465, 1895.

[150] Demant: Zeit. f. physiol. Chemie, Bd. x, S. 441, 1886.

[151] Langendorff: Arch. f. Physiol., Suppl. Bd., S. 269, 1886.

As to the causative influence of various diseases, Charrin and Carnot[134] produced diabetes by injecting diluted culture of bacillus pyocyaneus. Thomson, of Glasgow,[135] in a study of a large number of cases, found a large excess of sugar in children suffering from pertussis, epilepsy and convulsions, and a slight increase in cases of varicella, variola, enteric fever and peritonitis. Teschemacher[136] observed a case of measles in which the urine contained 4 per cent. of sugar. Mossé, Charles Blanc and others[137] observed it in cases of intermittent fever. Strümpell,[138] Dyce Duckworth[139] and many others refer to gout as a cause of transitory glycosuria.

In a large proportion of the cases met with, the glycosuria is due to the presence in the blood of an excess of normal physiological waste-products. These, by overstimulating the adrenal center, produce glycosuria in the same manner as thyroid extract and the other agents referred to above.*

The accumulation of these poisons is principally due to the ingestion of food in excess of the body's needs; excessive work is thus imposed upon the adrenal system and through it upon the pancreas.* Overeating becomes more active as a cause of glycosuria when, in addition, the blood is simultaneously being deprived, by the free use of alcohol, of some of the excess of oxygen the immunizing overactivity of the adrenal system is providing.* Hence, the fact that diabetes is usually observed in vigorous subjects who are large eaters, many of whom partake freely of alcohol.

All conditions which impose excessive wear and tear upon the body, prolonged overexertion, mental or physical, worry, anger,—which are all attended by an excessive production of toxic wastes—may also provoke diabetes through the same morbid process.*

This involves the conclusion that in this class of cases general metabolism must be correspondingly excessive. Lépine[140] states that it is a positive fact that in many cases of diabetes there is exaggerated destruction of nitrogen, a fact now generally recognized. Tyson[161] also says that the "urea is almost invariably increased," and considers as one of the causes of this symptom "the ingestion of large amounts of nitrogenous food, whether to appease the appetite or by the physician's advice."

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* *Author's conclusion.*

[132] Handfield Jones: Cited by F. Cartier: Thèse de Paris, 1891.

[133] Cartier: *Ibid.*, p. 15.

[134] Charrin and Carnot: C. r. hebd. des séances de la Soc. de biologie., 10 série, vol. i, p. 432, 1894.

[135] Thomson: Glasgow Hosp. Rep., vol. ii, p. 224, 1900.

[136] Teschemacher: Berl. klin. Woch., Bd. xxix, S. 33, 1892.

[137] Mossé, Charles Blanc, and others: Cited by Verneuil: Semaine méd., vol. viii, p. 298, 1888.

[138] Strümpell: Berl. klin. Woch., Bd. xxxiii, S. 1017, 1896.

[139] Dyce Duckworth: Lancet, Aug. 5, 1893.

[140] Lépine: Semaine médical, vol. xvii, p. 279, 1897.

A. Lorand, of Carlsbad,[162] also holds that diabetes is due to the fact that "people are taking more food, especially carbohydrate food, into their bodies than they can burn." As interpreted from my standpoint, it is the attempt to destroy the excess of wastes that this entails which causes glycosuria, the conversion of glycogen into sugar, glycosuria being in reality but one of the phenomena indicating that excessive metabolism is in progress.

The morbid influence of alcohol is illustrated by cases studied by Strauss of von Noorden's clinic[163] in which glycosuria followed the use of a mixed diet after a drinking bout. In one patient, who had lost the tendency to glycosuria after a carbohydrate diet without sugar, the glycosuria could be made to return by administering alcohol. Strümpell had already shown that alcohol favored the appearance of alimentary glycosuria.

The influence of physical strain, such as that caused by long tramping, is shown by five cases reported by Hoppe-Seyler,[164] in which rest caused the glycosuria to disappear. Gobbi[165] made a similar observation in eight runners who, before the race, had no sugar in their urine. Other instances of this kind have been reported. Mitra[166] states that diabetes is four times more prevalent in Bengal than elsewhere, and that it is practically limited to hard-worked professional men, officials and students. Bolye Chunder Sen[167] had already emphasized that while the country Hindoos were comparatively free from the disease, the proportion was large among the brain workers. Worms[168] found that among scientists and others leading intellectual pursuits, the proportion of diabetics was 10 per cent. in Paris, where, as shown by Bertillon, the mortality from diabetes had almost doubled between 1883 and 1892. Worms observed that the condition of diabetics was aggravated by worry.

The development of pathological changes in the organ which bears the brunt of the morbid process, the pancreas, occurs late in the history of the case. It is merely overworked, and is able to meet the needs of the stress imposed upon it. Glycosuria cannot, therefore, be attributed primarily to disease of the pancreas in this form of diabetes.* After a more or less prolonged period of overwork,* however, this organ begins to show morbid changes, though previously, and notwithstanding the presence of considerable sugar in the urine, and all the typical symptoms of diabetes, it had shown none whatever.

The general trend of the pathological process is a general degeneration of the pancreas, and more particularly as regards the glycosuria of the islands of Langerhans.

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* *Author's conclusion.*

[161] Tyson: "Practice of Medicine," third edition, p. 804, 1903.

[162] A. Lorand: Vermont Med. Monthly, Feb. 15, 1906.

[163] Strauss: Berl. klin. Woch., Bd. xxxvi, S. 276, 1899.

[164] Hoppe-Seyler: Münch. med. Woch., Bd. xlvii, S. 821, 1900.

[165] Gobbi: Riforma medica, Apr. 29, 1905.

[166] Mitra: Indian Med. Record, May 20, 1903.

[167] Bolye Chunder Sen: Indian Med. Gazette, July, 1893.

[168] Worms: Bull. de l'Acad. de méd., 3 série, vol. xxxiv, p. 169, 1895.

The first step is a general engorgement of the capillaries, which may be sufficiently marked in the more advanced cases to be accompanied by hæmorrhage, especially in the islands of Langerhans, in which these small vessels are extremely thin. The capillary walls then undergo hyaline degeneration, which gradually invades the islands and destroys them. In some cases, however, these structures become granular and undergo necrobiosis. Both these morbid processes may proceed to an advanced stage in the islands of Langerhans without involving the rest of the gland, or the latter may undergo atrophy and be replaced by fatty tissue. The local changes may also lead to a cirrhosis in which the secreting structures of the gland, as well as the islands of Langerhans, are gradually enmeshed in a fibrous network and obliterated.

The islands of Langerhans are the structures of the pancreas which yield first under the excessive stimulation to which the latter organ is subjected. Thus, a case of diabetes may proceed to a fatal termination through gradual degeneration of the islands and the other glandular elements be found normal after death. Moreover, these glandular elements may be profoundly diseased and no glycosuria occur.

Important in this connection is the fact that disease of the pancreas is not the cause of diabetes, as believed by many, and that the pancreatic lesions are due to overstimulation of this organ.*

As stated by R. H. Fitz,[169] the existence of pancreatic diabetes is established, but disease of the pancreas does not necessarily cause diabetes. Of 29 cases from the Massachusetts General Hospital that showed lesions of the pancreas, glycosuria was found in but 2, although in 12 cases there were no records of tests for sugar. The investigations of E. L. Opie[170] have thrown considerable light upon this problem. He not only pointed out that extensive lesions of the ordinary secretory structure with escape of the islands of Langerhans are unattended by diabetes, but also that destruction of the latter structures alone concurred with this disease. This is emphasized by the following details of an autopsy of a diabetic negress aged 54 years. The pancreas weighed 80 grammes, was soft and of a gray-yellow color. Almost every island of Langerhans showed microscopically a homogeneous material that stained with eosin. This substance at times lay in the midst of groups of cells, but was usually in contact with the walls of the capillaries penetrating the island, or next the peripheral fibrous tissue, and was, therefore, usually between the remaining cells and the capillary walls. The cells of the island were, in large part, replaced, so that between the hyaline particles only an occasional compressed fusiform or irregular nucleus could be seen. The hyaline metamorphosis was strictly limited to the islands of Langerhans, the glandular acini remaining intact. In this pancreas, therefore, a lesion of obscure etiology had destroyed the islands of Langerhans, while those of the secreting acini, as well as those of other organs, were unaffected. The association of diabetes mellitus affords convincing proof that the islands of Langerhans are intimately connected with the glycogenic metabolism.

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* *Author's conclusion.*

[169] R. H. Fitz: Yale Med. Jour., Mar., 1898.

[170] E. L. Opie: Jour. of Exper. Med., Mar. 25, 1901.

The fact that the pancreatic lesions are not the *original* cause of glycosuria, however, is shown by the many cases observed in which pancreatic lesions were either slight or absent. Thus, M. B. Schmidt[371] in 23 autopsies of diabetics found the pancreas entirely normal in 8 instances. It showed evidences of slight inflammation in 7, while in the rest there was either: *acute* interstitial inflammation, *chronic* interstitial inflammation or *hyaline* degeneration, which—from my viewpoint—represent steps of the degenerative process, followed in sufficiently vigorous cases by a reparative fibrosis. A. E. Finney[372] was also led to conclude, by a comprehensive study of the subject, that "diabetes may occur in the absence of demonstrable lesion in the islands of Langerhans." He also found that the injection of adrenalin chloride in the guinea-pig produced—besides general phenomena and hyperæmia of other organs—a peri-acinous engorgement of the pancreatic capillaries, the typical lesion to be expected in a condition brought about through excessive activity of the adrenal system.

There is, in the light of my views, as previously stated, another form of glycosuria, *asthenic* glycosuria, due to insufficiency of the adrenal system caused by poisons and diseases that *depress* the functional activity of either of its three organs, and thus lower oxygenation in the body at large.* The functions of the pancreas being inhibited thereby, overactivity of the islands of Langerhans plays no rôle in the pathogenesis of this stage.* This subject is treated below under a separate heading.

Treatment.—AGENTS WHICH REDUCE THE HYPERSENSITIVENESS OF THE ADRENAL CENTER.—If, as I would urge, diabetes mellitus is clearly differentiated from the form I describe below as pathogenically a totally different disease, it may be said that we possess a specific for each of these two affections.* Indeed, the test-organ and the adrenal center being overactive in diabetes mellitus, the remedy which suggests itself is that which serves physiologically in the body to subdue the functional activity of these organs,* namely, *arsenic*. That this remedy has proven of great value in a large proportion of cases is well known. The cause of its failure and of the harmful effects occasionally observed are accounted for, on the other hand, by the fact that it was given in cases of asthenic glycosuria, in which, as shown under the next heading, the adrenal mechanism is already markedly depressed.* In what might be termed sthenic diabetes, the form described above, however, it is of great value;* *Fowler's solution* may be given in 3-drop doses in a glassful of water during each meal, the dose being gradually increased until the first signs of the physiological effects of the drug appear, when it should be somewhat reduced. The object should be to keep the test-organ depressed until the excess of sugar disappears from the urine, and then to adjust the subsequent use of the remedy to this end.*

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* *Author's conclusion.*

[371] M. B. Schmidt: Münch. med. Woch., Bd. xlix, S. 51, 1902.

[372] A. E. Finney: Med. Chronicle, June, 1903.

Louis Lewis[173] ascribes the origin of the arsenic treatment of diabetes to Salkowski, who discovered that in animals poisoned by arsenic no artificial diabetes could be produced, either by puncture of the fourth ventricle or curare. Here the arsenic had evidently paralyzed the adrenal system and thereby the pancreatic functions. No amylopsin being produced, glycosuria failed to occur. Arsenic has been highly recommended by Dujardin-Beaumetz,[174] Jaccoud[175] and other authorities. Tyson[176] states that "after opium, arsenic has longest maintained its reputation as a remedy in diabetes," and that it seems to him that "there is something more than a simple tonic action in it."

Unfortunately, the patients become rapidly accustomed to the use of arsenic, and to offset this drawback, other agents having the same physiological action are indicated for a time. In some cases, the use of a different preparation of arsenic, the *bromide of arsenic, i.e.,* Clemens's solution, (administered in the same way as Fowler's, the dose being, on the whole, reduced one-third) suffices.* In others, the change does not affect the situation. The *sodium* or *strontium bromide* in 15-grain (1 gm.) doses on retiring, increased if necessary, and taken in a glassful of water, may then be used for a time—not more than a couple of weeks—then gradually reduced, while simultaneously the course of arsenic, beginning with 5 drops of Fowler's solution, is resumed.* When it becomes necessary again to withdraw the arsenic, *chloral hydrate* or *chloralamid* may be employed instead of the bromides or in conjunction with these salts, reducing the dose of each in proportion.* If the sugar in the urine can be kept down with smaller doses of these depressants, such doses should, of course, be used.*

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* *Author's conclusion.*

[173] Louis Lewis: Med. World, Oct., [illegible].

[174] Dujardin-Beaumetz: Bull. gén. de thérap., vol. cxvi, p. 241, [illegible].

[175] Jaccoud: Méd. moderne, vol. ix, p. [illegible], [illegible].

[176] Tyson: *Loc. cit.*, p. [illegible], [illegible].

It is obvious that the administration of any "tonic," "alterative," or "chalybeate," as recommended by some authors, must compromise the results.*

All these remedies have been used empirically for some time, as is well known. That they have been highly recommended by some and condemned by others is not strange, in view of the fact that while beneficial in sthenic glycosuria (diabetes), they are harmful in the asthenic form.

DRUGS WHICH TEND TO REDUCE EXCESSIVE TISSUE METABOLISM.—Remedies which, by exciting the sympathetic center only, but sufficiently to cause constriction of the arterioles, naturally reduce the volume of the blood supplied to all organs through their capillaries, and the intrinsic metabolism of these organs.* It is to this property that *opium* and *morphine* owe their beneficial effects.* A small dose of morphine, 1/8 grain (0.008 gm.), may be given twice daily, then three times daily. The dose is then increased to 1/6 grain (0.01 gm.) once in the day instead of the corresponding dose, then twice in the day, etc., the dose being increased and regulated according to the proportion of sugar in the urine. The danger of morphinism may, to a certain extent, be reduced by substituting *codeine* for a time, beginning with 1/4 grain (0.016 gm.) of the sulphate (not the phosphate, the preparation most used) three times daily. Opium or morphine, which are well borne by diabetics, are preferable, however; they diminish hunger because they reduce tissue waste by lessening the quantity of adrenoxidase admitted to the tissue-cells; they also cause a marked reduction of the sugar excreted, because the tissue carbohydrates, especially those of the muscular elements, are not as rapidly consumed.* The bowels should be kept open by means of *saline aperients;* the simultaneous free use of *Carlsbad water,* which contains sodium sulphate, bicarbonate and chloride, often suffices for this purpose, besides tending to preserve the blood's alkalinity.

Tyson states that "the only drug that can be relied upon to produce an effect in diminishing glycosuria is opium." Shoemaker[117] writes: "Opium is, perhaps, the most efficient drug which we possess in the treatment of this disorder. It diminishes hunger and thirst, the quantity of urine excreted, and the amount of sugar eliminated. The progress of the disease is checked and the condition of the patient ameliorated. Large doses are required and well-borne in diabetes mellitus."

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* *Author's conclusion.*

[117] Shoemaker: "Materia Medica and Therapeutics," sixth edition, p. 691, 1906.

If, for some reason, opium or its preparations cannot be continued, or given at all, *antipyrin and acetanilid* may be used instead, the initial dose being 10 grains (0.6 gm.)—with equal parts of sodium bicarbonate, three times daily, gradually increased if the sugar does not show a marked fall. We have seen that the effects of these coal-tar products are similar to those of opium, *e.g.*, they stimulate the sympathetic center and provoke constriction of all arterioles.* Another remedy which acts similarly is the *sodium salicylate* in doses varying from 10 to 15 grains (0.6 to 1 gm.) three times daily, but this remedy presents a drawback: it excites the test-organ sufficiently to counteract, at least partly, its beneficial effects.*

Antipyrin has been highly recommended by Dujardin-Beaumetz, Huchard, Robin and others. The first-named clinician noted that omission of the drug caused prompt recurrence of the sugar of the urine, both of which had been greatly reduced. Opitz[illegible] found antipyrin of great value also in cases of long standing. He gave 10 grains (0.6 gm.) t.i.d. and increased the dose by 5 grains (0.3 gm.) daily until 30 grains (2 gms.) were taken t.i.d., if necessary. The latter dose seems excessive, but it is generally recognized that these patients, as a rule, require large doses. The sodium salicylate introduced by Ebstein is mentioned because it has been found beneficial in some instances. I have never used it.

AGENTS WHICH INCREASE THE ALKALINITY OF THE BLOOD.—An important feature of this disease is the steady loss of the mineral constituents. Hence the fact that the blood's alkalinity is always low. When this condition is allowed to proceed, the acetone bodies accumulate in the blood, acetone, diacetic and oxybutyric acids appearing in the order named, according to the stage of the disease. Appearance of the two latter means that the patient is exposed to diabetic coma, owing mainly to the irritating influence of these two acids upon the kidneys. Now, sodium bicarbonate is known to offset and prevent coma, especially when given with large quantities of fluid. This is due mainly to the fact that, besides neutralizing the acids, the osmotic properties of the body fluids are restored to their normal condition, and that the catabolism of sugars and fats, as well as that of proteids, can be carried to a finish.* We should not wait, therefore, until these acids accumulate in the blood to utilize alkaline salts.

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* *Author's conclusion.*

[illegible] Opitz: Deut. med. Woch., Bd. xv, S. 648, 1889.

In the early stages, the use of an alkaline *mineral water* as a usual beverage (of which the patient usually partakes in large quantities), and the addition of an extra amount of *common salt* in his food suffice to preserve the normal osmotic properties of his blood—and, therefore, to insure adequate catabolism of sugars and fats,—thus preventing the formation of the pathogenic acids.* This process is aided materially by the free use of *green vegetables,* which are rich in potassium salts. In more advanced cases the addition of *sodium bicarbonate,* 20 grains (1.3 gms.) twice daily, dissolved in one glassful of the mineral water used, affords the additional alkalinity required. Or, *Vichy water,* the chief constituent of which is sodium bicarbonate, may be used as usual beverage.

The marked loss of mineral constituents by diabetics has been emphasized by Robin,[179] who found that the coefficient of demineralization sometimes attained 30 to 40 per cent. He found, as I have, that the patient fares better if encouraged to drink alkaline waters. Orlowsky[180] ascertained that the administration of alkalies increased the alkalinity of the blood and of its plasma to an appreciably higher degree than in healthy individuals.

Diet.—With hyperactivity of the test-organ and its adrenothyroid center as the direct factor in the overproduction of sugar, the prevailing method of depriving the patient of starches and sugars is unscientific.* The morbid process being an *excessive* consumption of these substances in the body at large, including the hepatic glycogen, their withdrawal from the food can have but one effect, viz., to place at the mercy of the amylolytic triad of the blood what carbohydrates remain in the tissues.* The body is thus depleted, as far as possible, of physiological components of the highest importance to its welfare. The sugar in the urine naturally diminishes, and may even disappear, but this does not prove in the least that the disease is counteracted; it only shows that the patient has been drained effectively of his main sources of muscular energy and heat. Nor does the meat diet to which the patient is relegated even protect him against the renal complications feared, since glycosuria is known frequently to persist under such a diet and to promote the appearance of acetonuria and acidosis. That abstention from starches, sugar, etc., is harmful under such conditions is shown by the fact that the restoration of carbohydrates often causes both acetonuria and acidosis to disappear.

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* *Author's conclusion.*

[179] Robin: Revue de thérap. méd-chir., vol. lxx, p. 297, 1903.

[180] Orlowsky: Vratch, vol. xxxii, pp. 1193, 1221, 1901.

But one carbohydrate, *usually wheat flour,* need, as a rule, be abstained from. Again, a large excretion of sugar occurs because the test-organ and its adrenothyroid center are hypersensitive.* The indications, therefore, in sthenic diabetes, are to seek the offending carbohydrate, forbid it, and reduce the total diet, in order to diminish as much as possible formation of *wastes which sustain the irritability of the test-organ.** Moreover, the diet should be varied, to avoid the presence in the blood of a relatively large proportion of any one waste. It is important to watch the urine for acetone and diacetic acid, which tend to bring on diabetic coma. Reduction of fats, the addition of a little bread, and sodium bicarbonate 15 grains three times daily, will, as a rule, cause the danger signals to disappear.

The true position of the dietetic measures usually recommended is well exemplified by Croftan's statement[illegible] that "with the introduction of calorimetric methods into the treatment of diabetes a new danger has arisen, viz., the substitution of a modern ultrascientific routine for the old-fashioned and venerable, but altogether unscientific, routine of feeding every diabetic ou a diet containing no starches or sugars." Stark[illegible] also wrote recently: "A rigid exclusion of sugars and starches in the treatment of diabetes is a thing of the past, nor do we often find it necessary to exclude them permanently from the menu of diabetes. On the contrary, we often substitute carbohydrates for fats in cases of marked acetonuria. . . . . . As a matter of fact, the organism actually requires for its maintenance carbohydrates for the repair and growth of its tissues, and for the production of heat and muscular force. This necessity for carbohydrates is so emphatic that directly they are prescribed the system draws upon the nitrogenous element of food to supply the missing component." As to the influence of meat, Croftan states that "in many cases it is well known that the sugar excretion only stops when the amount of meat is considerably reduced. Further, it can be shown that withdrawal or reduction of meat appreciably increases the tolerance of carbohydrates." He urges, moreover, that "the chief danger incident to complete withdrawal of carbohydrates is . . . *acidosis and coma,*" and also that "it is surprising how often the administration of a little carbohydrate in cases that are on a rigid diet, or of some more carbohydrate in cases that are receiving only small quantities of carbohydrate will cause all these dangerous phenomena to disappear." A lugubrious commentary upon the true meaning of all these facts is suggested by the case of a man in the last stages of the disease observed by Lépine, to whom sugar was granted owing to his hopeless condition, and who . . . . . began to improve. This suggested honey as an appropriate food, *i.e.*, *mel* in diabetes *mellitus*. The fallaciousness of the whole dietetic treatment based on old lines is emphasized by another method of which Hare[153] says: "Although potatoes are *eminently a starchy food*, recent investigations indicate that it is perhaps the best form of starch which can be taken by the diabetic." Mossé, who advocated this method, recommends that 2 or 3 *pounds* daily of this "eminently starchy food" be taken by the patient.

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* *Author's conclusion.*

[illegible] Croftan: Therap. Gaz., Apr. 15, 1908.

[illegible] Stark: Med. Record, Sept. 22, 1906.

Finally, the Hindoos and all vegetarians should show an enormous proportion of diabetics were the prevailing doctrine true. A Hindoo physician of wide experience, Bose,[154] states that the Jams, who are great starch and sugar eaters, and the Sadhoos, Jogees, and Chowbays of Muttra, who live upon sweets, do not suffer from diabetes. This does not mean that diabetes is not observed in India. A suggestive fact asserts itself in this connection, however: the patients live much longer in India, because, owing to their aversion for meat, they *cannot* be placed upon the "sugar- and starch-free diet."[155]

In the treatment of these cases, the following course is recommended: (1) Forbiddance of the offending carbohydrate, with reduction of diet and use of some plain alkaline mineral water: Ballardvale, Londonderry Lithia, etc.; (2) second week, arsenic added. If at the end of the third week the sugar is not reduced very considerably, acetanilid on retiring (besides preceding indications) with Vichy as beverage.* See also page 35, Vol. I.

ASTHENIC GLYCOSURIA.

SYNONYMS.—"*Toxic*" *Glycosuria*, but only as to depressing poisons (arsenic, chloral, etc.); "*Traumatic*," "*Shock*" and "*Fright*" *Glycosurias*; "*Diabetes Decipiens*;" "*Conjugal Glycosuria*;" "*Diabète Bronzé*" of the adrenal type; "*Diabète Maigre*" or "*Emaciating Diabetes*."

Definition.—A form of glycosuria due to poisons, diseases, traumatisms, shock, fright and other conditions which depress the functional activity of the test-organ or of the adrenothyroid and sympathetic centers of the pituitary body, and, therefore, the functional activity of all organs, including the pancreas. The secretory functions of this organ being inhibited, the formation of glycogen is correspondingly reduced, and the food carbohydrates which should be utilized in this function are directly converted into sugar in the alimentary canal and absorbed as such. Being unsuited for utilization by the tissues, this sugar is eliminated by the kidneys.**

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* *Author's conclusion.*

** *Author's definition.*

[153] Hare: "Practice of Medicine," p. 810, 1905.

[154] Bose: Brit. Med. Jour., Feb. 2, 1896.

[155] Editorial: The Antiseptic (Madras), Dec., 1905.

I find it impossible to avoid introducing the name "asthenic glycosuria." The term "toxic glycosuria" is sometimes employed to distinguish the form due to poisons from true diabetes mellitus. In the light of my views, however, it is faulty, since it includes two pathological processes which are not only distinct, but antagonistic. Thus, while strychnine and mercury provoke toxic glycosuria, by *stimulating* the adrenal system, arsenic, antimony, etc., bring it on by *depressing* the same system. Again, while the drugs which stimulate this system ultimately give rise to lesions similar to those observed in diabetes mellitus, those which depress it lead to organic changes of a special character, *i.e.*, those of arrested nutrition and atrophy. The term "asthenic" glycosuria seems to me not only to embody the essential feature of an autonomous morbid process, but also to suggest the appropriate line of treatment.

Alimentary glycosuria is not included in this form, since it may be produced through both hyper- and hypoactivity of the adrenal system.

Symptoms and Etiology.—While in the sthenic form, *i.e.*, diabetes mellitus, described in the preceding section, the type of patient is usually one indicating vigor and overactivity, in the asthenic form the opposite is the case.* The patient may be bulky and *obese,* but of the type denoting clearly general torpor and low vital activity. He may also be *thin,* delicate and anæmic, a class in which hypochondria and melancholia sometimes occur concurrently.

In the first volume[126] I advanced the view that there was also a form of diabetes due to insufficiency of the adrenal system and concluded[127] that "the glycosuria following extirpation of the pancreas is due to the action of the ptyalin upon food-starches." The latter conclusion was based on experiments by Aldehoff, Minkowski, Chittenden and Griswold, and von Mering and the well-known fact that, as stated by Howell,[128] "saliva or preparations of ptyalin act readily on boiled starch, converting it into sugar and dextrin." That amylopsin carries on, both in the intestine and elsewhere, the conversion of starches and glycogen into sugar is well known. The sugar produced, therefore, may be derived from that produced through the action of ptyalin and amylopsin, or directly—and mainly in asthenic glycosuria—from sugars ingested.

Howell also says,[129] referring to diabetes: "In severe forms of this disease, all the carbohydrate material of the food appears in the urine." That leucocytes take up food-stuffs from the intestine has been emphasized both in the first volume and the present one. In a recent paper, Pavy[130] states that he had[131] "adduced evidence to show that at the seat of absorption in the alimentary canal the carbohydrate is assimilated by synthesis into proteid through the instrumentality of the lymphocytes of the villi."

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* *Author's conclusion.*

[126] *Cf.* vol. i, p. 365.

[127] *Cf.* vol. i, p. 418.

[128] Howell: "T. B. of Physiol.," p. 679, 1905.

[129] Howell: *Ibid.*, p. 733.

[130] Pavy: Lancet, May 5, 1906.

[131] Pavy: "Carboh. Metab. and Diabetes," London, 1906.

Further evidence to the effect that the explanation I furnish of the pathogenesis of the asthenic form of glycosuria is sound, is afforded by the manner in which it harmonizes with the results of experimental observation, Lépine,[102] Bédart,[103] Thiroloix[104] and others having found that glycosuria did not follow removal of the pancreas in dogs deprived of food several days. The cause of this becomes obvious when the sugar is derived directly from the food-stuffs, as removal of the organ typifies, in the pathology of the disease, advanced organic changes in the pancreas. Lancereaux first pointed out in 1877 that the *diabète maigre* with which the asthenic type corresponds is invariably accompanied by pancreatic lesions. Saundby in his Bradshaw lecture[105] states that "in all typical cases of emaciating diabetes," the pancreas was in a shrunken state, and that they showed microscopically hyaline change and fibrosis. That general nutrition should be impaired under these conditions is self-evident. As de Dominici[106] says: "Destruction of the pancreas inevitably induces dystrophy of the organism in virtue of the absence of the very important functions of this organ in digestion, and in virtue of the absence of the substances that the pancreas produces, which regulates the equilibrium of metabolism."

That when the functions of the pancreas are inhibited by removal of this organ, glycosuria is produced, is well known. Minkowski found, and his results were confirmed by Hédon,[107] that when a fixed quantity of sugar was administered to animals after their pancreas had been removed, the sugar obtained from the urine was increased precisely in proportion with the quantity ingested. These and other experiments of a similar kind, clearly show that, as in the advanced stage of diabetes, the sugar eliminated is derived from the food and not from hepatic or tissue glycogen.

Adapting these facts to the forms I include under the term "asthenic glycosuria," we are brought to realize that hypoactivity of the adrenal system, *i.e.*, of the test-organ and the center through which it influences the adrenals and the thyroid—the adrenothyroid center—or of the thyroid and parathyroid glands; or of the adrenals or of the nerve-paths connecting any of these organs with one another—and whether due to organic lesions or to functional impairment of any of these structures—must, in turn, depress the secretory activity of the pancreas through the deficiency of adrenoxidase, and produce asthenic glycosuria by materially reducing the volume of amylopsin formed.

The diabetes ascribed to *syphilis* belongs to this group, and is apt to appear during the first four years, and in the course of the secondary and tertiary periods.* The so-called conjugal diabetes is, in reality, due to sexual transmission of the disease; the glycosuria of hereditary syphilis is also to be regarded as asthenic glycosuria.*

The glycosuria of alcoholism and influenza is essentially asthenic in character.* This applies as forcibly to the form observed in *neurasthenia* and after *cerebral hæmorrhage*, and,

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* *Author's conclusion.*

[102] Lépine: Lyon médical, vol. lxxvii, p. 335, 1894.

[103] Bédart: Le midi médical, Aug. 12, 1894.

[104] Thiroloix: C. r. hebd. des séances et mém. de la Soc. de biol., 10 série, vol. i, p. 297, 1894.

[105] Saundby: Birmingham Med. Rev., vol. xxviii, p. 129, 1890.

[106] De Dominici: Gazz. d. Osped., vol. xxiv, Pt. i, p. 630, 1903.

[107] Hédon: Arch. de physiol. norm. et pathol., 5 série, vol. v., p. 154, 1893.

obviously to the glycosuria of *senility,* and that due to excessive or too prolonged *lactation.** In individuals *who, in one way or another, show the* landmarks of *gout,* glycosuria is also asthenic *in character, while this* fact becomes self-evident in the *diabète bronzé* in which more or less advanced adrenal lesions are found, and which present many of the symptoms of Addison's disease.* *Shock* is another cause of this form of glycosuria, which may be attended by all the phenomena of diabetes, including a more or less rapid loss of flesh. *Grief, worry* and *exhaustion* may engender asthenic glycosuria, while anger and violent excitement may incite the sthenic type.*

An important form of asthenic glycosuria is that due to *traumatism.* In this class of cases sugar may appear as early as six hours after the receipt of the injury; but, as a rule, it begins in from eight to twelve hours. If it appears soon it is apt to be temporary, *i.e.,* to disappear within ten days. The interval between the accident and the appearance of sugar usually includes shock phenomena, more or less weakness, pallor, hypothermia, etc. This is followed by somnolence in some and insomnia in other cases, and leading at times to melancholia and other psychical disorders, especially in head injuries, which give rise to glycosuria oftener than others. Acetone and acetic acid are very rarely found in traumatic glycosuria except when it becomes permanent, and even then only when the case is advanced. Albumin, however, is always present.

The principal poisons which produce asthenic glycosuria in the same way are arsenic, antimony, curare, nicotine and the salts of uranium nitrate.*

A number of agents provoke the same functional inefficiency of the pancreas, and, therefore, asthenic glycosuria, indirectly.* Thus alcohol produces it by deoxidizing the blood; chloroform, ether and other anæsthetics, by reducing the intake of oxygen; amyl nitrite, chloral and chloralamid, by relaxing the arterial system and depleting the capillaries, including those of the pancreas; and, finally, morphine—a frequent cause of glycosuria—and caffeine, which, by causing marked constriction of the arterioles, reduce the quantity of blood admitted to all organs, including the pancreas.*

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* *Author's conclusion.*

That syphilis is a cause of glycosuria is familiar to every one. Ord[198] and Trollet,[199] however, emphasized the fact that it occurred with relative frequency during the third stage—that attended by the greatest adynamia. Tchistiakoff[200] found also that the urine presented no other abnormal constituent. This serves to differentiate asthenic glycosuria from that of diabetes in which phosphoric acid, etc., and other evidences of exaggerated metabolism are present.* Again, as suggested by Trollet, such cases account for the so-called "conjugal diabetes," which thus becomes conjugal syphilis with diabetes as a normal consequence. Schnee,[201] moreover, has traced it to inherited syphilis. Suggestive also is the fact that this form of diabetes promptly yields to antisyphilitic treatment, *i.e.*, to mercury and the iodides—both most powerful adrenal stimulants, and which, therefore, most vigorously counteract the asthenia.* Stress was not only laid on this fact by Seegen, Servantie, Tchistiakoff, Decker[202] and others, but the last-named observer found that recovery ensued without modifying the diet.

As stated by Ebstein,[203] obesity, gout and diabetes are closely related, and any two or all three of them may be present in the same person. Hirschfeld[204] not only observed this close relation between obesity and diabetes, but also that obese people showed sugar after a meal containing a fairly large quantity of sugar. In the concomitant presence of obesity and gout we have evidence of deficient metabolism, and in the post-prandial glycosuria a strong probability that the sugar is derived directly from the food-starches.

The concurrence of glycosuria with neurasthenia has been frequently observed by Landon Carter Gray.[205] Influenza, a disease in which general neurasthenia is marked, may also be followed by severe glycosuria, as observed by Magelson,[206] Holsti,[207] Broadbent[208] and others. In the latter observer's case, which was already of three years' standing when reported, there was weakness and abolition of the knee reflex.

As to drugs, arsenic, which, we have seen, is an efficient remedy in true diabetes, is a pernicious agent in asthenic glycosuria. Claude Bernard, Saikowski, Quinquaud and Masoin[209] all found that it was even capable of preventing the glycosuria produced by puncture of the bulb. Latham[210] first reported cases of glycosuria caused by arsenic. The reason for this is plain, when we recall that arsenic is the physiological antagonist of the thyroid secretion. That alcohol can cause glycosuria is generally recognized. As emphasized by Sandras and Bouchardat, however, large doses are required. Von Noorden[211] considers chronic alcoholism a prominent cause. Chloroform was found by Winterstein[212] to reduce in animals the intake of oxygen; Ebstein[213] observed a very great aggravation in a practically cured case through the use of chloroform as an anæsthetic. Bendix gave dogs large quantities of grape sugar, but found none in their urine; a similar experiment followed by chloroform anæsthesia, caused the appearance of glycosuria in all the animals. Similar experiments with morphine led to identical results. This agent was found by Eckhardt[314] to readily provoke glycosuria; F. Cartier[315] states that from 0.03 to 0.06 gm. (½ to 1 gr.) never fails to produce it in the rabbit; he refers to a case of Gilbert's in which morphinomania gave rise to continuous glycosuria. The other drugs mentioned as causes are represented by desultory cases in literature.

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* *Author's conclusion.*

[198] Ord: Brit. Med. Jour., Nov. 2, 1889.

[199] Trollet: Thèse de Paris, 1905.

[200] Tchistiakoff: Wratch, Nos. 4, 5, 1894.

[201] Schnee: Inter. klin. Rundschau, Sept. 20, 1888.

[202] Decker: Deut. med. Woch., Bd. xv, S. 944, 1889.

[203] Ebstein: *Ibid.*, Bd. xxiv, S. 693, 1898.

[204] Hirschfeld: Med. News, Jan. 28, 1898.

[205] Gray: Med. Record, May 12, 1894.

[206] Magelson: Med. News, Oct. 10, 1891.

[207] Holsti: Zeit. f. klin. Med., Bd. xx, S. 272, 1892.

[208] Broadbent: Lancet, Sept. 15, 1894.

[209] Claude Bernard, Saikowski, Quinquaud and Masoin: Cited by Cartier: *Loc. cit.*

[210] Latham: "Facts and Opinions Concerning Diabetes." London, 1811.

[211] Von Noorden: Berl. klin. Woch., Bd. xxxvii, S. 1117, 1900.

[212] Winterstein: Cited by Bendix: Centralbl. f. Stoffw. u. Verd. Krankh., Bd. iii, S. 149, 1902.

[213] Ebstein: *Ibid.*

Pathogenesis and Pathology.—The disorders, diseases or poisons which provoke asthenic glycosuria include those which greatly depress the functional activity of the test-organ, the adrenothyroid center, or any of the organs of the adrenal system; or those of the vascular centers: the sympathetic and vasomotor.[*] The oxygenation of the blood or the access of the blood to the various organs being impaired, their functions and nutrition are correspondingly inhibited.[*] The pancreas being included among the organs thus affected, its output in ferments—including the active agent in the conversion of glycogen to sugar, amylopsin—is greatly diminished.[*] The pancreas is reduced, therefore, as far as its functions are concerned, to the condition which prevails in the advanced stage of diabetes mellitus.[*] While in the latter disease the pancreas is destroyed organically through excessive intrinsic metabolism, in asthenic glycosuria it may be only functionally paralyzed, owing to inadequate oxygenation and local hypometabolism.[*]

The sugar originates, therefore, as may be the case in advanced diabetes, directly from the sugar ingested or from food-starches, the conversion occurring in the alimentary canal. This sugar, being taken up by the digestive leucocytes, is unloaded by these cells in the intercellular spaces, but being in excess of the needs of the tissues, the surplus is carried by the lymph-stream to the blood.[*] The glycolytic property of this fluid enables it to destroy a part of this sugar, but the bulk of it, to prevent hyperglycæmia, is promptly excreted by the kidney.

The presence in some cases of bronzing, as in Addison's disease, *i.e.*, the diabète bronzé of Hanot and Chauffard (1882), clearly points to adrenal insufficiency. Their opinion that cirrhosis of the liver is always present has been invalidated in recent years, Abbott,[316] Murri,[317] Rabé[318] and others having reported cases in which it did not prevail.

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[*] *Author's conclusion.*

[314] Eckhardt: Beiträge z. Anat. u. Physiol., 1877.

[315] F. Cartier: *Loc. cit.*

[316] Abbott: Jour. of Path. and Bact., Dec., 1900.

[317] Murri: Med. Woche, Mar. 24, 1902.

[318] Rabé: Presse méd., vol. ix, p. 183, 1902.

Auscher, Gilbert, Opie, Chauveau and Kauffmann and others have met the issue by considering the glycæmia as a simple complication of hæmochromatosis. But the cause of the latter phenomenon was left unanswered. This answer is afforded, however, by inhibition of the adrenal functions. Not only is bronzing caused, as is well known, by such a condition in Addison's disease, but we have seen that removal of these organs produced hæmochromatosis, and as shown by the experiments of Boinet, a general invasion of the whole organism by bronze pigment. The adrenals themselves may be involved in the process, as shown by cases reported by various observers. In a case of diabetes reported by Kuhn[229] coinciding with cancer of the breast, the right adrenal was found to be the seat of metastasis. Barth,[230] de Massary[231] and many other observers have reported cases of glycosuria in which bronzing was present. Lépine[232] observed a marked case of diabetes and hyperglycæmia in which the right adrenal was the seat of a large sarcoma. Mimi[233] observed a typical case in a woman whose entire body, except the soles and palms, was bronzed.

In keeping with this class of cases are the many in which lesions of the sympathetic paths and ganglia are present, thus interrupting the impulses from the pituitary body to the adrenals. Thus, Saundby[234] refers to 4 cases in which the semilunar ganglia were found diseased. Thiroloix, Sandmeyer,[235] Cavazzanni[236] and others have since reported cases in which the sympathetic structures were deeply involved.

Myxœdema, interpreted from my standpoint,[237] is the typical syndrome of failure of the adrenal system. Talbot Jones,[238] in a clinical paper, concluded over ten years ago, that "there are striking pathological analogies between true diabetes and myxœdema," and that "in the latter disease, success has also attended both injections and thyroid grafting—a success achieved not only in animals, but also in man." That the two conditions may occur simultaneously is shown by 2 cases reported by A. Gordon[239] in brothers, in both of which thyroid extract proved highly beneficial. Conversely, we have seen by the cases of Ewald and Strasser that when glycosuria does not exist in such cases it may be brought on by giving thyroid extract, *i.e.*, by stimulating too vigorously a torpid adrenal center.* This involves an important distinction when treatment is to be instituted. We will see that it is only in the asthenic type that thyroid extract is indicated, and that as observed by Murrell[240] "its administration should be maintained just as in myxœdema."

The asthenic glycosuria due to traumatism is the result of concussion of the *sensorium commune, i.e.*, the aggregate of highly differentiated centers of the posterior pituitary, of which the sympathetic center is the most sensitive.* As a result of this concussion and the general shock it entails, the vessels are relaxed, and, blood accumulating in the larger vessels and depleting the capillary system, the functions of the pancreas and liver, among other organs, are inhibited.* Traumatic glycosuria may be temporary, but it may also persist and ultimately terminate the patient's life, owing mainly to gradual atrophic degeneration of the pancreas similar to that observed in asthenic glycosuria due to other causes.*

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* *Author's conclusion.*

[229] Kuhn: Münch. med. Woch., Bd. xlix, S. 103, 1902.

[230] Barth: Bull. de la Soc. anat., vol. lxii, p. 560, 1888.

[231] de Massary: *Ibid.*, vol. lxx, p. 504, 1895.

[232] Lépine: Revue de méd., vol. xxvi, p. 537, 1906.

[233] Mimi: Rev. crit. de clin. méd., Mar. 16, 1901.

[234] Saundby: *Loc. cit.*

[235] Sandmeyer: Münch. med. Woch., vol. xxxviii, p. 309, 1891.

[236] Cavazzanni: Centralbl. f. allg. Pathol. u. pathol. Anat., Bd. iv, S. 501, 1893.

[237] *Cf.* vol. i, p. 174 *et seq.*

[238] Talbot Jones: Med. Record, May 23, 1896.

[239] A. Gordon: Amer. Medicine, Feb. 6, 1904.

[240] Murrell: Med. Press and Circular, Dec. 14, 1896.

Injuries may also, by causing concussion of the pituitary body and inhibition of what functional activity a diseased pancreas may still retain in an advanced case of diabetes,* hasten the fatal termination of that case.

That general concussion—including the most delicate centers of the organism, those of the pituitary body—should attend traumatisms is suggested by the general asthenia observed in such cases. The prominence of nervous phenomena, which has caused this form of glycosuria to be included among the traumatic neuroses, points in the same direction. Ebstein,[881] in reporting a case of fatal diabetes due to a general concussion received during a railway accident, concluded after a comprehensive study of the subject, that "numerous cases recorded in medical literature show that between trauma and diabetes, as well as between trauma and functional disturbances of the nervous system, there exists a causal relation." If we were dealing with cerebral concussion, mental phenomena should develop at once in every instance; but such is not the case. The unconsciousness of shock is due to depletion of the cerebral vessels, somnolence likewise, melancholia to hyponutrition—all conditions which bring us back to the sympathetic center. We have seen also that in acromegaly all disorders of sensibility are traceable to the neural lobe of the pituitary body. As stated by Bernstein-Kohan,[882] after a study of 45 cases, disturbances of sensibility are frequently observed in cases of diabetes following injury. That fatal diabetes may occur without injury of the bulbar centers is illustrated by a case of Vogel's mentioned while discussing a paper by Ziemssen[883] in which it followed the fall of a beam on the neck. The glycosuria which appeared a few weeks after the injury was ascribed to concussion of the spinal cord, though no lesions were found in this organ or in the medulla. That its governing center, the pituitary body, should have borne the brunt of the shock seems logical in view of the fact that the slightest irritation of this organ, as shown by the experiments of Cyon and Masay,[884] will bring about widespread vascular phenomena.

It is generally impossible to assert that sugar was not present in the urine before the injury was received. Loisnel[885] reported a case, however, in which the urine had been examined—owing to a slight gastric disorder—with negative result, two months before the injury, a fall on the back, was received. Within a few weeks after the latter, glycosuria developed and the patient died of diabetic coma two months later. In such a case the slow—and many of the same kind are available in literature—process of hyaline degeneration and fibrosis of true diabetes has no time to occur.

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* *Author's conclusion.*

[881] Ebstein: Deut. Archiv f. klin. Med., Bd. liv, S. 305, 1895.

[882] Bernstein-Kohan: Thèse de Paris, 1891.

[883] Ziemssen: Münch. med. Woch., Bd. xxxvi, S. 17, 1889.

[884] Cyon and Masay: *Cf.* this vol., p. 962.

[885] Loisnel: La normandie médicale, vol. vii, p. 145, 1891.

The entire history of such cases points to shock and inhibited function and nutrition. Suggestive in this connection is the fact that traumatisms of the head are more frequently followed by glycosuria than when located elsewhere. In Bernstein-Kohan's series of 45 cases, 25 were due to head injuries. Higgins and Ogden,[236] in a study of 212 reported cases of traumatism of the head, found that glycosuria had been present in 20.

Asher[237] and other authors place the spine and sacral region immediately after the head. Shock, asthenic and inhibited function are well exemplified by one of von Gadden's[238] cases, a fall on the head—there was extreme weakness and emaciation. Immediately after the fall, the patient suffered from intense thirst, and his urine contained 7 per cent. of sugar.

That shock and inhibited function are also the pathogenic factor in true diabetes is also shown by recorded cases. Spitzer,[239] for example, instances a woman who had suffered from diabetes for five years, and who developed coma three hours after fracturing her clavicle; sodium bicarbonate administered in large doses did not prevent a fatal issue. Litten[240] reported the case of a diabetic who fell and bruised his testicle; some days afterward he developed acute digestive symptoms, and died of coma ten days after the accident.

Fright usually causes but a temporary glycosuria. Lorand,[241] however, reported two cases which proved fatal: one in a woman of 35 years, who had been well before the fright was experienced. Weakness appeared the same day; polyuria and glycosuria (7 per cent.) five days later, followed by death in one year. The second occurred in a girl of 16 years, also in perfect health before the fright. Soon afterward gastric disorders and emaciation occurred and her urine ultimately showed 8 per cent. of sugar. The case proved fatal in a few months.

The history of these cases clearly points to the nature of the morbid process. As stated by Herter[242] in respect to the glycosuria following head injuries, it must be assumed either that the pancreas is also involved, or that the circulation in the liver has been permanently changed in such a way that no carbohydrate can be stored. Interpreted from my standpoint, the *central* shock impairs the nutrition of the pancreas, and its functions being inhibited, the alimentary starches are directly converted into sugar and eliminated precisely as is the case after removal of the pancreas.

It is in this form of glycosuria that the pancreas is often found free from lesions post-mortem, while in the cases of relatively prolonged duration, the organ presents all the evidences of atrophy.

The absence of lesions of the pancreas in cases of diabetes has led Hansemann[243] to classify them separately. As such a group would contain cases of incipient diabetes as well as cases of asthenic glycosuria, such a subdivision is not desirable. Nevertheless, it emphasizes the fact that glycosuria is often unaccompanied by pancreatic lesions. William-

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[236] Higgins and Ogden: Boston Med. and Surg. Jour., Feb. 28, 1895.

[237] Asher: Vierteljahresschrift f. gericht. Med. u. Sanitätswesen, Bd. viii, S. 219; Bd. ix, S. 1, 1895.

[238] von Gadden: Friedreich's Blätter f. gerichtl. Med. u. Sanitäts-Polizei, Bd. 1, Hft. 1, 1899.

[239] Spitzer: Deut. med. Woch., Bd. xxvi, S. 756, 1900.

[240] Litten: Soc. méd intern. de Berlin, Apr. 29, 1901.

[241] Lorand: St. Petersb. med. Woch., Jahrg. xxviii, S. 223, 1903.

[242] Herter: Med. Record, Feb. 9, 1901.

[243] Hansemann: Zeit. f. klin. Med., Bd. xxvi, S. 191, 1894.

son[244] in a series of 15 cases in which autopsy was performed with especial care, macroscopically and microscopically found the pancreas normal in 7 instances and the seat of simple atrophy in 2. In 23 autopsies mentioned by M. B. Schmidt[245] the pancreas was normal in 8 and markedly atrophied in only 1 instance. Mollard[246] also reported a case of wasting diabetes in which the pancreas was found in a perfectly healthy condition.

Treatment.—That the indications in asthenic glycosuria should be precisely the converse of those of the sthenic type, diabetes mellitus, is now self-evident.* *Thyroid gland* irrespective of the cause of the asthenia may be given in 1 grain (0.06 gm.) doses three times daily.

The failure of the adrenals also indicates the need of compensative treatment. This is best supplied by means of the *hypophysis sicca* (U. S. P.) which from my viewpoint owes its lasting effects to the adrenal constituents the posterior lobe of the pituitary contains. It may be given in 1/10 grain (0.0016 gm.) doses three times daily during meals, along with the thyroid gland.

The use of thyroid gland in glycosuria has been practically abandoned, owing to the fact that it increased the excretion of sugar in many instances. The reason for this is self-evident in the light of my views: it was used empirically, and as the majority of cases of glycosuria are of the sthenic type, the trouble was aggravated. In true asthenic cases, however, it is quite effective. Thus, Lépine[247] obtained marked improvement in the case of an obese patient, although at first the sugar increased. In a case due to shock, in which considerable loss of flesh and the typical symptoms of diabetes were present, Murrell[248] obtained marked benefit from thyroid, but its use had to be persisted in as in myxœdema. Under its use health was maintained, though the patient "did not diet herself." J. McNamara[249] found that thyroid extract was able to cause disappearance of the sugar in such cases, several of which he had had occasion to treat. He concluded that, inasmuch as there was diminution of fat, the thyroid produced its beneficial effects by promoting metabolism.

A striking confirmation of the value of adrenal stimulants in a class of cases which can only be of the asthenic type* is afforded by the recognized efficiency of *potassium iodide* in some cases, especially those clearly traceable to syphilis. An important distinction is necessary here, however. We have seen that large doses, by sensitizing the depressor nerve, inhibit the functions of the pituitary body and of the thyroid apparatus.* The best effects are obtained in asthenic glycosuria by giving small doses of iodide, namely 5 grains (0.3 gm.) in a glassful of water after meals, and gradually increasing the dose until 10 grains (0.6 gm.) are administered in the same manner.* The *biniodide of mercury* is preferable when the centers require more active stimulation, $^1/_{16}$ grain (0.004 gm.) three times daily, carefully watched, to prevent salivation.*

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* *Author's conclusion.*

[244] Williamson: Lancet, Apr. 14, 1894.

[245] M. B. Schmidt: *Loc. cit.*

[246] Mollard: Lyon médical, vol. lxvi, p. 229, 1891.

[247] Lépine: Semaine médical, vol. xviii, p. 497, 1898.

[248] Murrell: Med. Press and Circular, Dec. 14, 1898.

[249] J. McNamara: Lancet, July 18, 1903.

The statement in text-books that iodine or the iodides should not be given after meals because it forms an iodide of starch with that contained in bread, vegetables, etc., is not sustained clinically. I have seen iodism caused by one-drop doses of pure iodine thus given. The value of the iodides in the syphilitic form of diabetics requires no evidence. This applies as well to the use of mercury, which, as is well known, increases promptly the functional activity of the pancreas (by increasing general metabolism, I would add), the end in view.

The diet should in no way be reduced in such cases, unless some carbohydrate, whether starch or sugar, be found to sustain the glycosuria, the aim being to enhance the vital process. Tonics are in order, especially *strychnine* and *quinine*, which stimulate both the vascular and adrenal centers.* The *desiccated adrenal gland* (*glandulæ suprarenales siccæ* of the U. S. P.) is very effective in these cases. The best results are obtained when the diagnosis of asthenic glycosuria has been carefully established, by giving the *thyroid gland,* 1 grain (0.06 gm.) *adrenal gland,* 2 grains (0.13 gm.) and *strychnine,* $^1/_{40}$ grain (0.00165) together in a capsule, during, *i.e.,* in the middle of each meal.

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* *Author's conclusion.*

CHAPTER XXVII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

THE ADRENAL SYSTEM IN THE INFECTIOUS DISEASES OF THE LUNGS.

Tuberculosis, unlike cancer and pneumonia, shows a steadily diminishing mortality, thanks mainly to the painstaking labor that has been devoted to its prophylaxis. About one death in seven is still due to this fell disease, however, and when the fact that it assails mainly adolescents and young adults is taken into account, it may, without reserve, still be regarded as the greatest enemy of mankind.

That the adrenal system plays a rôle of the greatest magnitude in the cure of tuberculosis was suggested in the first volume. As to predisposing conditions, I stated (1903) therein:[1] "Insufficiency of the adrenals" . . . . "by reducing the oxidation processes correspondingly reduces the nutrition of the pulmonary tissues: a predominating feature of phthisis;" again:[2] "It is not in the lungs, therefore, that the primary endogenous cause of the disease must be sought, but in the adrenal system." As to the mode of infection, I emphasized the fact[3] that "as soon as the tubercle bacillus is admitted, it becomes an additional source of adrenal insufficiency" through toxins "which react upon the anterior pituitary body precisely as would any other equally virulent poison." As to treatment, I urged that "medication calculated to raise or develop the functional activity of the adrenal system to a high standard must, in the light of the views submitted, not only prevent the development of pulmonary or any other form of tuberculosis, but arrest it in its earlier stages." The rôle of Koch's tuberculin in the diagnosis and cure of the disease was also stated[4] to give rise to a "febrile reaction when a tuberculous process is present, because it adds to the toxic elements incident upon the disease, a new source of adrenal activity." . . . . "Spurred to unusual energy by the tuberculin, the adrenal system excites a correspondingly active metabolism in all cellular structures, including those endowed with leucocytogenesis. Phagocytes and alexins are produced in profusion, the fixed endothelial and the connective-tissue cells contributing their share to the production of the latter, and there is thus constituted a serum which confers upon the treated individual a degree of immunity commensurate with the degree of the reaction produced in the adrenals."

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[1] *Cf.* vol. i, p. 478,
[2] *Cf.* vol. i, p. 773, } in the first two editions.
[3] *Cf.* vol. i, p. 775,
[4] *Cf.* vol. i, p. [illegible] et seq.,

All these statements were published in January, 1903. We have seen how accurately the able researches of Sir A. E. Wright harmonize with and sustain them, though this observer was unaware of the source of the "internal secretion" which he considers as the "bacteriotropic" or immunizing substance, which accumulates in the blood after tuberculin inoculations. We will now see that the views I advanced over four years ago are sustained by the suggestive fact that they account for every phase of the morbid process and for many isolated experimental and clinical observations which have only tended—without the adrenal system—to increase the complexity of the question as a whole.

The evidence submitted in the following pages appears to me to show conclusively that the disease *is not the unconquerable foe that it is generally thought to be,* and that with the adrenal system as the foundation of the curative process, and remedies which, as I have shown, can control the workings of this system, and through it the body's bacteriolytic and antitoxic agents, we can and should curb the disease and finally obliterate it.

PULMONARY TUBERCULOSIS.

SYNONYMS.—*Consumption; Phthisis; Phthisis Pulmonalis.*

Definition.—Tuberculosis is due primarily to the presence and multiplication in the body of Koch's bacillus tuberculosis. Its characteristic phenomena are provoked by two endotoxins which the dead body of this bacillus liberates: (1) a poison *of unknown identity which depresses directly the test-organ and through it the adrenal system, thus inhibiting the protective functions of this system; (2) a nucleo-proteid rich in phosphorus which, when in contact with pulmonary or other living tissues, abstracts their oxygen, thus forming areas of necrosis. The tubercles which characterize this disease are coverings for* the necrosed areas and the remnants of the pathogenic organisms, but which, if some of the bacilli be still living, may become centers of infection.**

Symptoms and Pathology.—The early signs usually described are in reality those of a fully developed disease, when local lesions are sufficiently marked to compromise the issue. A more or less purulent expectoration, the hæmorrhages, etc., point to a process of disintegration, *i.e.*, to a period in which infection has made considerable headway.

Notwithstanding the diagnostic value of the tubercle bacillus, to await the demonstration of its presence in the sputum, as is so often done, before establishing a diagnosis, is to compromise the patient's life.

When the symptoms are such as to suggest the need of examining the sputum, they are sufficiently threatening to impose upon the physician the duty of instituting *at once* measures that will tend to arrest the lethal trend. The absence of tubercle bacilli in the sputum does not prove the absence of the disease.

The *incipient* or *first* stage is due primarily to *insufficiency of the ductless glands*. Hence the lowered nutrition of the body at large, as shown by a more or less rapid *emaciation*, general *weakness* and several other early symptoms. There is often marked *pallor* of the skin and mucous membranes, especially those of the palate and larynx; a tendency to *hypothermia* (replaced by fever when the morbid process is more advanced), cold extremities and sensitiveness to cold, particularly in young girls and children, the temperature declining one or two degrees (F.) at various times of the day, or remaining low, days, or even weeks, at a time; a febrile *tachycardia*, the pulse being from ten to twenty beats higher than normal, associated with *lowered blood-pressure* and, in cases in which the latter symptom is marked, passive *sweating*.

That the deficient nutrition is primarily due in this disease to an inadequate supply of adrenoxidase* is shown by the readiness with which such a condition accounts for the symptoms. Thus, a deficiency of oxygen, by reducing the functional activity of all organs, must inhibit digestion, leucocytosis, and reduces, therefore, the amount of food taken by the leucocytes from the alimentary canal and carried to the tissues, thus causing emaciation.* The muscular tissues being insufficiently nourished, weakness follows. The muscular coats of the arteries and veins being similarly influenced, they relax, causing lowering of the blood-pressure, while this fall, in turn; causes acceleration of the heart's action (Marey's law), *i.e.*, tachycardia.* When the muscular debility is excessive, relaxation of the spiral muscles of the sweat-glands gives rise to sweating—especially at night, when all the muscular elements are most relaxed.* All these symptoms are also due in part to the recession of blood from the periphery and its accumulation in the large internal vessels, especially those of the splanchnic area, as a result of the general vasodilation.* The capillaries of the skin being thus rendered ischæmic, the pallor, hypothermia, sensitiveness to cold, etc., are markedly aggravated.*

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* *Author's conclusion.*

** *Author's definition.*

Of all these symptoms, those most frequently met with during the incipient stage are the rapid pulse and tachycardia, emaciation, pallor of the skin and mucous membranes, slight cough and lassitude. When they are encountered in a subject predisposed to the disease through inheritance, or who has been exposed to contamination, the case should be considered as one of tuberculosis as far as treatment is concerned.* The diagnosis becomes positive, however, irrespective of the absence of tubercle bacilli, when in addition to these signs, the muscular atrophy is sufficiently marked to cause cog-wheel inspiration, *drooping of the shoulders,* with diminished expansion especially marked in the infraclavicular space, and abnormal projection of the scapulæ; and if, moreover, one of the *tuberculous stigmata,* a long, narrow, cylindrical or flat thorax, cutaneous tuberculosis, anal or ischio-rectal fistulæ and especially *enlarged axillary glands* in adults and the *tracheo-bronchial* glands in children, is present.*

These various phenomena (those given in italics) constitute collectively an autonomous symptom-complex differing from the stage next to be described in that every symptom exemplifies organic weakness. The incipient stage, therefore, is essentially one of functional depression.*

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* *Author's conclusion.*

The emaciation, weakness, anæmia and pallor are familiar symptoms owing to their persistence throughout the disease. The important feature in this connection, however, is to detect them before the onset of the pulmonary lesions.

That impaired nutrition is closely related with an abnormal state of the blood is shown by the state of the latter. Grawitz[5] found that at the *onset* of the disease, there was diminution of the red corpuscles. Rachford[6] in 41 convent girls exposed to tuberculous contagion averaged 63 per cent. of hæmoglobin; he asserts that pronounced anæmia in young convent girls of tuberculous stock warrants a diagnosis of tuberculosis. Appelbaum[7] found that particularly in tall, rapidly growing youths with a poorly developed chest "anæmia is present in the first stage of tuberculosis; the erythrocytes are diminished in number, the hæmoglobin is reduced, the specific gravity is lessened and *coagulation is delayed.*" Ullom and Craig[8] also found that before the formation of cavities, the decrease of erythrocytes and a relatively greater decrease in hæmoglobin were constant. Hypothermia, cold extremities, etc., are a normal outcome of such a condition; as observed by Weill,[9] Vargas and Négrié[10] and others, it is especially marked in children and adolescents. Holmes[11] regards the "subnormal morning temperature" as an important sign.

The diminution of the general nutrition is made evident not only by emaciation, but often by atrophy of the muscles. Bompard[12] observed diminution of volume, subsidence of prominences of the body, exaggeration of hollows, loss of strength and diminution of electrical contractility, and advises chamber gymnastics "to combat this form of muscular debility, which is common particularly at the outset of the disease." Carcassonne[13] illustrated by a number of cases that atrophy of the scapulo-thoracic muscles was evident before percussion or ausculation revealed any sign of tuberculosis. De Renzi and Coop,[14] by means of Mosso's myotonometer, found the muscular tonicity reduced from the start, even though nutrition appeared normal. Cecconi[15] claims that it announces an early active manifestation of the disease.

The heart is influenced in the same manner, as shown by its diminution in size. This phenomenon, first observed by Laennec, has ever since occupied a prominent place in the pathology of tuberculosis. Louis,[16] who found it in 109 out of 112 cases, Bizot, Rokitansky, Brehmer[17] and other equally prominent clinicians have, in fact, attributed phthisis to its influence. G. W. Norris[18] in an able paper on the subject, referring to post-mortem findings at the Phipps Institute, states that they tended to show that "in uncomplicated cases of pulmonary tuberculosis, the heart is subnormal in size in quite a considerable number of cases," an observation also strongly sustained by a fluoroscopic study of 90 cases by Bouchard and Balthazard.[19] Norris lays stress, moreover, on the fact that "the heart of tuberculous individuals is often small, not as the result of hyperplasia, but from *atrophy* or *degeneration* of its substance." This fact, he adds, "has long since been sufficiently pointed out by Louis, Andral, Kidd, Bennet, Quain, Strumpell, von Leyden, and has been observed by all who have given attention to the matter." That deficient general nutrition is the underlying cause of this condition has been emphasized by Brehmer, Potain and others.

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* *Author's conclusion.*

[5] Grawitz: Deut. med. Woch., Bd. xix, S. 1347, 1893.

[6] Rachford: N. Y. Med. Jour., Aug. 10, 1895.

[7] Appelbaum: Berl. klin. Woch., Bd. xxxix, S. 7, 1902.

[8] Ullom and Craig: Amer. Jour. Med. Sci., Sept., 1905.

[9] Weill: Lyon méd., vol. lxxvi, p. 77, 1894.

[10] Vargas and Négrié: La Semaine méd., vol. xv, p. 387, 1895.

[11] Holmes: Phila. Med. Jour., Aug. 19, 1899.

[12] Bompard: Jour. de méd. de Bordeaux, Nov. 13, 1887.

[13] Carcassonne: Arch. gén. de méd., vol. clxxxv, p. 226, 1900.

[14] De Renzi and Coop: Trans. Tuber. Congr., Naples, 1900.

[15] Cecconi: Trans. Tuber. Congr., 1905.

[16] Louis: "Recherches sur la Phthisie."

[17] Bizot, Rokitansky, Brehmer: Cited by Norris: Amer. Jour. Med. Sci., Oct., 1904.

[18] Norris: *Ibid.*

Interpreted from my standpoint, an additional cause for the smallness of the heart prevails. A prominent symptom of the incipient stage, we have seen, is a low blood-pressure. Thus, Marfan[20] found it subnormal in 97 per cent. of the cases examined. Goodno[21] also states that while "the normal pressure in a healthy man is 15 to 18 c.m., in incipient tuberculosis it falls to 13, 12 or even 10 c.m.,—a fact noted by many investigators. If we recall that this entails accumulation of the blood in the great central trunks, *i.e.*, the splanchnic area, at the expense of the peripheral circulation, it will become apparent that the volume of blood which the heart has to transmit to the periphery each time it contracts, must be correspondingly reduced. As a result its expansion or diastole is diminished (its systole being commensurate with the reduced volume of blood) and it carries on its functions in this semi-contracted state months, and doubtless years in most instances.[*] That it should be found in this state *post-mortem*, especially when inadequately nourished during a corresponding period, is self-evident.

The rapid pulse or tachycardia, a sign to which many clinicians, including Potain, Leyden, Cornet and Loomis, attach great importance, is closely related to this process. It is a constant accompaniment of low blood-pressure, the two phenomena being related through a nervous mechanism. Thus, Leonard Hill[22] states that "if," as pointed out by Marey,[23] "all the cardiac nerves be intact, a rise of arterial pressure always slows the heart, and a fall accelerates it." The nature of this functional relationship asserts itself when the reduced volume of blood projected by the heart with each systole is taken into account: it is to *compensate* for this reduced quantity that the cardiac pulsations are reflexly increased, the purpose being to raise the quantity of blood passed through the lungs within a given time up to the normal standard.[*]

The accumulation of blood in the large trunks of the splanchnic area by depleting the peripheral capillaries is, aside from the diminution of red corpuscles and hæmoglobin, an important factor in the production of all symptoms of the incipient stage, *i.e.*, pallor, hypothermia and chilliness, muscular weakness and atrophy—besides the tachycardia in which, we have seen, it plays a leading rôle.[*]

This general adynamia is the result of two concurrent factors: the first of these is the presence in the tubercle bacillus of a toxin (an endotoxin, since it is active after death of the bacillus) which depresses the sensitiveness of the test-organ.[*] The functional activity of the adrenal system being inhibited in proportion, general metabolism is inadequate.* This entails also deficient formation of auto-antitoxin and a corresponding fall of the bacteriolytic and antitoxic properties of the blood.*

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[*] *Author's conclusion.*

[19] Bouchard and Balthazard: Revue de la tuberculose, T. x, p. 1, 1903.

[20] Marfan: La semaine méd., vol. xi, p. 213, 1891.

[21] Goodno: Medical Era, July, 1899.

[22] Leonard Hill: Schäfer's "T. B. of Physiol.," vol. ii, p. 56, 1900.

[23] Marey: "La circulation du sang," Paris, p. 334, 1881.

This is well shown by the preliminary effect of tuberculin, as demonstrated by Sir A. E. Wright, who states,[illegible] referring to his own observations: "Upon the inoculation of the vaccine there supervened a period of intoxication which is characterized by a *decline* in the anti-bacterial power of the blood. This negative phase is more or less prolonged according as a larger or smaller dose of the vaccine is inoculated." That this action is due to active depression, by the germ or its endotoxin, of organic functions is made apparent by the fact that, as stated by Professor Lukis[illegible] in reference to Wright's investigations: "It is found that injection of small doses of Tuberculin T. R. [an emulsion of dead tubercule bacilli] causes first a temporary fall in the opsonic index, lasting from a few hours to as much as 14 days, and that this fall is followed by a prolonged rise. This action is presumably exactly the same as that caused by the products of bacterial activity in the course of phthisis, the characteristic feature of which is that in the early stages you find periods of activity alternating with periods of quiescence, these alternations being associated with corresponding variations in the opsonic index." These alternations are characteristic of the reactions of the adrenal system, as we have seen under Epilepsy. We will see, moreover, that a similar accumulation of wastes, besides detritus incident upon the tuberculous process, accounts also for the reaction stage caused—indirectly—by tuberculin. That the direct action of tuberculin is to depress the test-organ, is shown by the fact that De Vecchi and Bolognesi[illegible] found that after inoculation with tuberculous material, the chromatophile cells of the pituitary body showed evidence of *hypo*-function.

The second cause of adynamia is due, even in this, the incipient stage, to the presence in the lungs of sufficiently advanced lesions to reduce markedly the intake of oxygen.

Insidiously, or giving rise perhaps to a slight though *stubborn reflex cough,* tubercle bacilli have been, for some time before the symptoms enumerated appear at all, destroying the functional activity of the air-cells or alveoli. Here they caused the formation of tubercles, small nodules varying in size from that of a pin-point to that of a millet-seed. Located from the first in the delicate partitions that separate the minute saccules or air-vesicles of an alveolus, they gradually increase in number until the latter and the terminal bronchiole leading to it are filled with them. As tubercles are being formed simultaneously in many alveoli, entire lobules (which contain several alveoli) are finally rendered useless, the respiratory area of the region involved being reduced in proportion. Hence the presence of another major symptom, when the breathing area is sufficiently compromised, viz., *dyspnœa*, which occurs at first only during physical exertion.

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* *Author's conclusion.*

[illegible] Sir A. E. Wright: Lancet, Dec. 2, 1905.

[illegible] Lukis: Calcutta Med. Jour., Apr., 1907.

[illegible] De Vecchi and Bolognesi: Riforma méd., Aug. 19, 1905.

The development of the tubercle is primarily due to the local irritation which the bacilli excite in the connective tissue and epithelial elements. The irritated spot attracts numerous leucocytes, many of which, the polynuclears (some being phagocytes), supply the trypsin and nucleo-proteid which, with the adrenoxidase and thyroidase secreted by the red corpuscles, form auto-antitoxin.* The evident purpose of this process is to destroy the germs.*

The tuberculous process *per se*, *i.e.*, the formation of the tubercle, is due to the disintegration of the bacilli in the alveolar walls by the local bacteriolytic elements, and to the liberation of their main endotoxin,—a substance which enters into the composition of these germs, and *the active principle of which is phosphorus.** So great is the proportion of this element in the solids of tubercle bacilli that their ashes contain over 60 per cent. of phosphoric anhydride. The morbid process is aggravated, moreover, by the fact that these bacilli actively reduce the adrenoxidase at the expense of the tissues.*

Maffucci, of Pisa,[27] found that culture preparations of tubercle bacilli contained, when the bacilli were dead, a toxic substance which resists the action of time, heat, desiccation, sunlight and gastric juice. He ascertained, however, that it is not a product of bacillary secretion, nor derived from the nutrient medium, but a *poison* in the substance of the bacillus itself, and liberated when the germ is disintegrated. A minute dose of this poison sufficed to cause "marasmus" and simultaneously inflammation and necrosis of the tissues, and other lesions typical of tuberculosis and anæmia. On the other hand, Hammerschlag showed that the bacilli produced an extract which contained lecithin (a body containing considerable phosphorus) capable of producing death in rabbits and guinea-pigs, while Levene[28] found that the body-substance of the tubercle bacillus not only contained phosphorus, but a body rich in this element: nucleo-proteid. The most valuable of these researches, however, are those of G. E. de Schweinitz and Marion Dorset.[29] They analyzed the ash of tubercle bacilli to the amount of 1453 grammes after the manner prescribed for plants, and found that it contained 55.23 per cent. of phosphoric anhydride (P_2O_5), a proportion which was raised to 60.90 in a subsequent analysis by de Schweinitz. This obviously indicates that pure phosphorus enters for a large share in the composition of these germs. When the rapidity with which they multiply is taken into account, it becomes evident that under conditions that favor their proliferation in the body they constitute a prolific source of phosphorus.

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* *Author's conclusion.*

[27] Maffucci: Il Policlinico, vol. ii, p. 1, 1895.

[28] Levene: Med. Record, Dec. 17, 1898.

[29] de Schweinitz and Dorset: National Med. Rev., May, 1898.

That tubercle bacilli are pathogenic owing to their phosphorus (doubtless in loose combination with other constituents) is shown by the similarity of their effects to those of chronic phosphorus poisoning. Phosphorus, as is well known, arrests local nutrition. While Cau[50] and others found that this was due to oxidation of the element, Araki[51] showed that lack of oxygen was a prominent feature of general phosphorus poisoning. This observation, according to Cushny,[52] "confirms the impression of many earlier writers." This author also states that "as soon as it is oxidised, phosphorus loses its specific action"—thus restricting to the element itself the morbid phenomena witnessed. Comparing these phenomena with those of the incipient stage of tuberculosis—due, in my opinion, to the bacterial (a loosely combined) phosphorus—the analogy is striking. The coagulation-necrosis caused by the tubercle bacillus is a counterpart of that caused by phosphorus. As to the anæmia and diminution of red corpuscles and hæmoglobin, Vogel,[53] d'Amore and Falcone[54] and others have recorded similar effects in phosphorus poisoning. The low blood-pressure and rapid heart-beat are likewise present in the latter condition, as observed by Pouchet and Chevalier,[55] who also noted that large doses of phosphorus (orthophosphoric acid being used) more than doubled the heart-beats. Precisely as is the case in tuberculosis, Pal[56] found that the low blood-pressure was due to dilation of the vessels. Magitot[57] includes among the symptoms of chronic poisoning in French match-factories, wasting of the tissues.

That it is the oxygen of the adrenoxidase that is consumed in the process is also evident. We have seen that Appelbaum found that in tuberculosis the coagulation of the blood was delayed—a phenomenon due to deficiency of coagulating ferment, *i.e.*, adrenoxidase; now Cevidalli[58] also found "diminution and disappearance of the coagulating ferment" in slow phosphorus poisoning, while Araki[59] observed that the coagulability of the blood was so reduced in some instances that it remained fluid forty-eight hours or more.

The formation of the tubercle, therefore, requires the death of the bacilli, thus liberating their principal constituent, phosphorus.* This element, owing to its intense affinity for oxygen, becomes oxidized at the expense of what adrenoxidase may be present, but when this source fails, it takes up that of the underlying cellular elements (of the previously irritated area) and provokes a local coagulation necrosis.* Hence the almost invariable absence of even dead bacilli in the necrotic center of the tubercle, though they may be present in large quantities in the immediate neighborhood.* This central area contains, however, granular masses composed of disintegrated cell-nuclei and the remains of necrotic tissue. Surrounding it is the so-called "granulation-tissue" zone which in reality is mainly composed of the leucocytes previously referred to and their used products. Thus, the framework of this zone is a network of fibrin, a substance formed, we have seen, when nucleo-proteid and fibrin ferment (adrenoxidase) combine to form a clot.[*] In this network are imbedded the leucocytes, remnants of fibrous tissue, granulation cells and their nuclei, the whole forming around the necrotic focus a loose capsule which gradually fades into the surrounding normal tissues or, as is usually the case, merges with adjoining tubercles.

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* *Author's conclusion.*

[50] Cau: Thèse de Paris, 1901.

[51] Araki: Zeit. f. physiol. Chem., Bd. xvii, S. 311, 1892-93; Bd. xix, S. 422, 1894.

[52] Cushny: "Pharm. and Therap.," third edition, p. 603, 1899.

[53] Vogel: Arch. inter. de pharm. et de thérap., T. x, fasc. iii et iv, 1902.

[54] d'Amore and Falcone: Arch. de pharm. de Gand, vol. i, p. 247, 1894.

[55] Pouchet and Chevalier: Bull. gén. de thérap., vol. cl, p. 915, 1905.

[56] Pal: Wiener klin. Woch., Bd. ix, S. 909, 1896.

[57] Magitot: Therap. Gaz., Sept. 16, 1895.

[58] Cevidalli: Riforma medica, vol. xviii, Pt. iv, pp. 686, 690, 711, 1902.

[59] Araki: *Loc. cit.*

This entire process is an inflammatory one from start to finish.[*] This is further shown by the presence in most instances, of giant-cells, which occur in other conditions as sequels of inflammation. They consist of a large mass of protoplasm containing numerous nuclei, and are similar to the giant-cells of bone (osteoclasts) known to be phagocytic. As they surround the tubercles, and project pseudopodial processes into them, while, moreover, they often contain detritus, bacilli and disintegration products of the latter, their evident function is to act as phagocytes in order to remove, if possible, the tubercular mass.

If this auto-protective process fails to be carried out successfully,[*] as is often the case in animals, and when the formation of tubercles is rapid, the central necrotic mass becomes caseous, a feature which tends to cause confluence of a group of tubercles. Under these conditions a more active auto-protective process is awakened,[*] *i.e.*, fibrous encapsulation. This is brought about by the growth, around each tubercle or aggregate of tubercles, of cellular connective tissue which gradually becomes more fibrous as its cells disappear. Connective tissue bands and a thick, fibrous network soon invest the entire tuberculous mass, enclosing necrotic tissues, cell-remnants and even the giant-cells, in their grasp. The caseous material dries and shrinks, and is finally transformed into a calcareous and gritty mass enclosed in a fibrous cicatrix, which sometimes includes considerable of the surrounding tissues.

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[*] *Author's conclusion.*

The large proportion of phosphorus that the tubercle bacilli contain has suggested that their pathogenicity might be due to the need of phosphorus as food. The fact, however, that they are far more pathogenic when dead, conclusively eliminates such a conclusion.

Koch[40] showed that dead tubercle bacilli, when injected subcutaneously in guinea-pigs, produced an abscess. Prudden and Hodenpyl[41] not only confirmed this result, ascribing the action to a "bacterio-protein" liberated when the bacilli were disintegrated in the tissues, but they obtained, after intraperitoneal or pleural injections of an emulsion of bacilli, nodules of various dimensions. The center of these nodules, composed of epithelioid and giant cells, contained tubercle bacilli in abundance, imbedded in creamy material and surrounded by fibrous tissue. This was confirmed by Straus and Gamaleia,[42] by Vissman,[43] who concluded that "tubercle bacilli, though dead and therefore deprived of the power of growth and metabolism, can still originate alterations in the tissues resembling in every detail the structure of a fresh tubercle;" by Alfred Masur,[44] whose experiments showed that "the bodies of dead tubercle bacilli contained toxic substances which are to be regarded as the cause of the changes in the diseased organs;" and finally by Stewart Stockman,[45] who found that the soluble products of the tubercle bacillus produce little effect on the healthy organism and that the dead bacilli are far more active than the soluble products.

Again, if these lesions are due to the phosphorus of the disintegrated bacilli, they should correspond with the local changes produced by this element. Referring to phosphorus, Cushny[46] writes: "Another feature in phosphorus poisoning, which is, however, better seen after *repeated small doses* than after a single large one, is the proliferation of the interstitial connective tissue of the stomach, liver and kidney, which finally induces typical cirrhosis of these organs." Baumgarten,[47] on the other hand, defines a tubercle as "the result of proliferative and exudative changes." Cushny also says, referring to the action of phosphorus *vapor*, that "many pathologists now regard this proliferation as a secondary result of the *necrosis* of parenchyma cells." Abel,[48] on the other hand, "by the injection of dead tubercle bacilli into the tracheas of rabbits, found, after twenty-four hours, white isolated areas in the bronchi and alveoli made up of round cells, among which were the bacilli; twenty-four hours later these were *necrotic* and epithelial proliferation had begun." E. R. Le Count,[49] from whose paper Abel's lines are quoted, remarks: "Thus we find, in marked contrast to one another, a *liquefactive necrosis*, which we recognize under the more common term of suppuration, *formation of fibrous tissue* and a *necrosis without liquefaction*—three distinct processes differing from one another anatomically and histologically, and having for their etiological factor the poisonous substances present in the bodies of the dead tubercle bacilli." These three processes are also peculiar to chronic phosphorus poisoning, the liquefactive necrosis being especially marked in osseous tissues. Le Count also states that fibrin (composed, we have seen, of nucleo-proteid and adrenoxidase) is "constantly present" in the tubercles of guinea-pigs, and that "the frequent presence of fibrin in genuine tubercle nodules in human beings has been demonstrated by Werneck de Aquilar in Baumgarten's laboratory." The presence of fibrin is, in fact, generally mentioned in text-books. Even the fibrous encapsulation of the tubercle finds its counterpart in the fibrous indurations which terminate the curative process in lesions caused by phosphorus.

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[40] Koch: Deut. med. Woch., Bd. xvii, p. 101, 1891.
[41] Prudden and Hodenpyl: N. Y. Med. Jour., June 20, 1891.
[42] Straus and Gamaleia: Arch. de méd. expér., vol. iii, p. 705, 1891.
[43] Vissman: Albany Med. Annals, Dec., 1893.
[44] Alfred Masur: Münch. med. Woch., Bd. xlii, S. 249, 1895.
[45] Stewart Stockman: Brit. Med. Jour., Sept. 3, 1898.
[46] Cushny: *Loc. cit.*, fourth edition, p. 593, 1906.
[47] Baumgarten: Cited by Falk: Virchow's Archiv, Bd. xxxix, S. 319, 1867.
[48] Abel: Deut. med. Woch., Bd. xviii, S. 482, 1892.
[49] Le Count: Jour. of Exp. Med., Nov. 1897.

Suggestive in this connection is the predilection of matchworkers to phthisis. J. Ewing Mears[30] states that "in many there is observed a gradual deterioration of physical condition as manifested in loss of flesh and vigor." In the only three fatal cases to which he refers, "the immediate cause of death was phthisis." Ralph Stockman[31] states that the phosphorus fumes to which match-workers are exposed "consist of phosphorous anhydride (P_4O_6) and some phosphoric anhydride (P_2O_5)"—the latter being the form found in the ashes of tubercle bacilli by de Schweinitz and Dorset, as we have seen. After referring to the cases in which necrosis affects only the jaw-bones, and which recover after surgical intervention, he writes: "In other cases, the disease, instead of healing, spreads locally, involving more bone, the patient becomes cachectic, feverish, and wasted, and ultimately dies of pulmonary phthisis, general tuberculosis or some other tuberculous affection." Convinced by this, and by the fact that, as he states, "the condition generally is *exactly similar* to what is seen in *tuberculosis* of the jaw in cattle and in tuberculous disease of other bones in man,"* he concluded that the cause of phosphorus necrosis was the tubercle bacillus, and examined the pus from six cases by the Ziehl-Neelsen method, finding it in each instance. He says, however, that "the organisms were few in number and difficult to find except on the closest and most careful examination;" that even after centrifugalization and utilization of the sediment "sometimes several coverglasses had to be examined before any of the organisms were seen," and finally that "inoculation of guinea-pigs with the pus did not infect these animals with tubercle."

In view of the data I have submitted in the foregoing pages and the fact that, as stated by Abbott,[32] "there is a group of bacilli whose numbers are in many respects so like the genuine bacillus tuberculosis as easily to be mistaken for it," and which are "characterized by the same staining peculiarities," while "not all members of this group are capable of causing disease," the germs observed by Ralph Stockman evidently belong to this benign class. Indeed, it is doubtful whether cases of chronic phosphorism are even as vulnerable to infection as the average individual, owing to the immunizing influence of their febrile state. On the other hand, when we consider (1) that as Stockman says, "the accounts of post-mortem examinations of fatal cases" show that "in *most cases* death occurs from tuberculosis of the lungs" in match-workers, and that the fumes of phosphorus which they inhale months, or years, finally provoke a general disease so similar to pulmonary tuberculosis, that it becomes a question whether the bacillus of this disease is not its true cause, and (2) that the pathogenic agent of the tubercle bacillus, in the light of the evidence adduced, is phosphorus, the conclusion seems warranted that tuberculosis is a phosphorus necrosis of the pulmonary tissues, and that the tubercle is naught else than a capsule for the necrosed area, calculated to isolate it from the surrounding normal tissues.

The *second stage* becomes clearly defined when the deposit of tubercles is sufficiently great to modify the normal sounds obtained from the chest by auscultation and percussion.

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* The italics are my own.—S.

[30] J. Ewing Mears: Trans. Amer. Surg. Assoc., vol. III, p. 257, 1885.

[31] Ralph Stockman: Brit. Med. Jour., Jan. 7, 1899.

[32] Abbott: "Principles of Bacteriology," seventh edition, p. 363, 1905.

The formation of the tubercles usually begins in the pulmonary structures below the apex of either lung (not necessarily the left, as generally believed), or of both lungs simultaneously, behind the middle of the clavicle. When sufficient area is involved, reliable physical signs may be detected on auscultation immediately below the clavicle, above it, and over the supra-spinous fossa posteriorly, namely, *roughness of the inspiratory murmur,* coupled with *lowering of its pitch,* and; when the respiratory field is greatly reduced in the area examined, *muffling of the vesicular murmur* with prolonged or *blowing expiration.* These modifications are mainly due to the reduction of the caliber of the bronchioles and of the secondary air-passages in the cavity of the alveoli, by the tubercles. The detection of these signs is facilitated by comparing the sounds heard with those of some other part of the lung, especially the other lobes which are seldom involved early in the disease. It is also only when considerable lung tissue is involved that *dullness on percussion,* the pitch of the notes being somewhat raised, and *increased vocal resonance*—the denser tissues being better sound-conductors—become clearly defined. The *cough* in this stage is marked in proportion as the various factors which oppose the elimination of the excrementitious materials pent up in the alveoli, bronchioles and the rest of the bronchial passages—viscidity, mechanical obstruction, etc.—are great. The sputa at this time often contain small grayish-green masses which originate from the diseased area and are composed mainly of tubercles, broken-down leucocytes, and fibrin. Sputum of this kind usually contains *tubercle bacilli.*

Dyspnœa, especially marked on exertion, and *increase of the respiratory rate* are prominent symptoms of this stage. They are due not only to the diminution of the respiratory field owing to obliteration of the air-cells by the tubercles, but also to the deficiency of hæmoglobin, the oxygen intake satisfying the needs of the body only when it is in repose. *Lassitude* also becomes more marked, owing to the increased muscular weakness. The latter condition may now cause interrupted or *cog-wheel inspiration,* the muscles being too weak to expand the chest, and doing so by jerks instead of by means of their usual imperceptible contractions. Another result of muscular weakness is *dyspepsia,* the muscular layers of the stomach being unable adequately to churn its contents and insure its passage through the pylorus.* This symptom is materially aggravated by the deficiency of pepsin—due to the deficiency of oxygen in the blood and the resulting torpor of all cellular functions, including, of course, those of glandular organs. *Diarrhœa,* owing to this morbid condition of the muscular, glandular and epithelial elements of the intestinal canal, may also occur: a prototype, to a certain extent, of the bronchorrhœa so often mistaken for bronchitis.* In young girls, the same general adynamia shows itself by *absence* or *diminution of menses,* and in a large proportion of cases by *anorexia*—an additional source of emaciation and debility.

Fever is another important symptom of the second stage. That it is partly due to auto-protective overactivity of the adrenal system excited by the pulmonary lesions, is shown by the fact that although it is of a continued type, it is attended with evening exacerbations, the fever ranging between 99.5° and 100.5° F. (37.50° and 38° C.), until it assumes the hectic type. It is aggravated, as shown under Treatment, by vascular hypertension.* In markedly debilitated individuals the fluctuations may range from a subnormal temperature of 96.5° F. (35.8° C.), for instance, to 99° F. (37.2° C.). The brightness of the patient's eyes is often sufficiently marked to suggest this febrile condition. Profuse *night-sweats* are commonly observed during this stage, but, as in the first stage, they are the result of the nocturnal depression and relaxation of the spiral muscles of the sweat-glands, the temperature being subnormal.

Hæmorrhage from the lungs is of frequent occurrence during this stage. It is rarely profuse, being due to involvement in the necrotic process of an area of capillaries or of some small arterial twig. Although it should excite suspicion when no other symptom of tuberculosis is present, it does not necessarily indicate the presence of this disease, since it can also be due to cardiac disorders, vicarious menstruation, naso-pharyngeal ulceration, sarcoma of any portion of the respiratory tract, aneurism, arteriosclerosis and other conditions. Its occurrence with loss of weight, dullness at either apex and increased vocal resonance, however, suggests tuberculosis.

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* *Author's conclusion.*

Hoarseness is occasionally the initial symptom, but ultimately develops in a large proportion of cases. It points generally to involvement of the larynx in the tubercular process, and entails considerable suffering. The larynx should be examined, and if local tuberculosis is to develop, the tissues overlying the arytenoid cartilages or the epiglottis will appear œdematous and swollen. Spots of ulceration may also be present, but these are more apt to occur in the interarytenoid space. *Pains* in various parts of the chest, changing from one place to the other, but frequently located in the back and in the region of the scapula, are sometimes complained of. *Pleurisy* is a frequent complication owing to contamination through contiguity; it is also characterized at the outset by pain.

In doubtful cases, when all other means of diagnosis have been exhausted, *tuberculin* may be tried. Its mode of action will be reviewed under Treatment.

The *diazo-reaction* of Ehrlich is of but little value, being often obtained in other diseases and only in tuberculosis when the morbid process is sufficiently advanced to be readily recognized by ordinary methods. This latter conclusion is also applicable to the x-ray method.

Concerning the presence of lesions in both apices, singly or jointly, Tyson[53] states that Osler "out of 413 cases found the right apex involved in 172; the left in 130; both, in 111." He also refers to T. G. Davis, who, out of 94 cases, found the lesions markedly worse on the right side in 39, and on the left side in 29, while both sides were affected in 26.

The value of inspiratory roughness pointed out by Grancher has been generally recognized. It is harsh and rasping and is best heard when the patient takes a deep breath, and leans against some support. It is considered by Grancher, Landouzy, Marfan and equally competent clinicians as positively indicating the onset of tuberculosis, especially when emaciation and pallor are also present. Grancher[54] ascribes it to obstruction of the alveolar vestibule by the developing tubercles, and contends that dullness, upon which so much reliance is placed, occurs only when consolidation is advanced. Pye Smith[55] in fact considers it an even more tardy sign. That the cog-wheel, interrupted respiration means atrophy of the muscles was emphasized by Liebermeister[56] and others.

The frequency of laryngeal lesions in pulmonary tuberculosis is shown by the fact that Stein[57] found them in 170 cases out of 474 examined. J. Payson Clark[58] also found the nasal mucous membrane atrophied in 70 cases out of 100 examined and holds that it precedes the pulmonary lesions. Enlarged axillary glands, varying in size from a pea to a hazel-nut, and rolling under the finger, as pointed out by Fernet,[illegible] are often present very early when progressive emaciation without apparent cause proves to be tuberculosis.

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[53] Tyson: "Pract. of Med.," third edition, p. 254, 1903.
[54] Grancher: Le bull. méd., vol. ix, p. 815, 1895.
[55] Pye Smith: Lancet, Apr. 7, 1900.
[56] Liebermeister: Deut. med. Woch., Bd. xiv, S. 789, 1888.
[57] Stein: Hospitalstidende: Bd. xiii, S, 787, 865, 1905.
[58] Payson Clark: Boston Med. and Surg. Jour., Oct. 3, 1895.

Trudeau[illegible] found the tuberculin test generally reliable when in suspected cases the diagnosis could be established by no other means. This represents the consensus of opinion of the many clinicians who have used it extensively.

In the *third stage*, that of softening of the tubercles and cavity formation, areas of caseation in the lung tissue varying from the size of a pea to that of a lobe, or even an entire lung, are formed when the necrotic process is too rapid to permit the formation of the fibrin network or outer zone which in the miliary tubercle encloses the necrotic tissues and the disintegrated bacteria. Hence the fact that the caseous masses are found to contain a large number of tubercle bacilli. A caseous mass is a compound of necrosed pulmonary tissue destroyed by the bacilli, and of the constituents of the auto-antitoxin (now minus its oxygen) accumulated in the corresponding area to destroy these germs.* It indicates that the auto-protective process was inadequate to counteract their development, a fact which accounts for the presence of intact bacteria.* When the masses are not too large, they may undergo calcification or fibrous encapsulation, as in the second stage, both of which are curative processes. Such a fortunate result takes place when the auto-protective resources of the body become sufficiently active from one cause or another to carry it on to a finish.* The diseased tissues are thus completely isolated from the normal parenchyma.

When spontaneous cure fails to occur, the caseous masses soften and are more or less perfectly expelled by way of the bronchi, with which they usually communicate, leaving a cavity. The destructive process continuing in the walls of the latter, however, it is gradually enlarged, and as many undergo this process simultaneously they eventually merge, forming larger cavities. As the tubercle bacillus is the source of all this destruction, the process is one of continuous tissue necrosis, the detritus of which represents morphologically the contents of a large abscess—but minus the pus organism. There comes a time, however, when these organisms are likewise present as prominent factors of the suppurative process, which now becomes one of *mixed infection*, with more or less septicæmia as a consequence.

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* *Author's conclusion.*

[illegible] Fernet: Bull. de l'Acad. de Méd., Mar. 10, 1903.

[illegible] Trudeau: Inter. Med. Mag., Mar., 1900.

The apex being the starting point of the cavity-formation, a large vomica may be present in this location, while the lower lobe, which the destructive process is gradually invading, is still the seat of smaller cavities. Sometimes the periphery of the lung is reached, and if it happens to be beneath the pleura, pneumothorax occurs.

Around cavities of all dimensions, especially beneath the pleura, there is clear evidence of an effort to protect contiguous structures, connective tissue being developed to limit their extent. An entire apex may thus be isolated, its numerous cavities being enclosed in dense masses of fibrous tissue—evidence to the effect that even at this advanced stage of the disease, much can be done to arrest the lethal trend.*

That calcareous or sclerotic masses are frequently found *post-mortem* in persons who were free from tuberculosis at the time of their death has long been known. Schlenker found that 65 per cent. of 100 autopsies, irrespective of the cause of death, showed evidences of tuberculosis; Biggs found them in 60 per cent., and in another series, 31.5 per cent. of 4000 autopsies; and Naegeli, 97 per cent. of 500 autopsies.[61] Vibert,[62] in looking over the register of necropsies made at the Paris Morgue, was "struck by the fact that in 131 individuals of from 25 to 55 years of age, having all succumbed to violent or sudden deaths, it was noted that the existence of pulmonary tuberculosis was recognized in 25, in 17 of whom the malady was in a cretaceous, or healed state." Rogée and Bondet, in their anatomical studies of the subject at the Salpêtrière and Bicêtre Hospitals in Paris, among aged subjects, found that the proportion of instances in which there was clear evidence of spontaneous arrest of the disease was as high as four-fifths. Aupinel,[63] in the course of 60 autopsies in aged individuals who had died of various diseases, found evidences of cured tuberculosis in *every instance*, and concluded with Cruveilhier, Cornil and Ranvier, Bollinger and others, that few persons escape infection, but that, thanks to calcareous infiltration and fibrous encapsulation, the lesions are spontaneously healed in most instances.

The general phenomena of the third stage are chiefly characterized by their intensity. The *emaciation* has become very marked and the general *weakness* correspondingly so. The *cough* is not only much more severe, but deprives the patient of sleep by its persistence; moreover, the ingestion of food, by causing severe accesses of coughing, provokes emesis, at times of an entire meal. The *expectoration* is now profuse. The sputum is purulent and contains irregular, tough, roundish masses that tend to adhere to the edges of the vessel, the "nummular" or coin-like sputa. These are characteristic in that they are similar to the contents of the cavities, containing innumerable bacilli, pus-cells, epithelial cells, elastic tissue from the disintegrated alveoli, broken-down leucocytes, etc., and —an important feature in view of the rôle of phosphorus in the morbid process as I interpret it—an abundance of phosphates.

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* *Author's conclusion.*
[61] Schlenker: Cited by Hare: "Pract. of Med.," p. 306, 1905.
[62] Vibert: Lancet, Sept. 22, 1888.
[63] Aupinel: Thèse de Paris, 1895.

Hæmorrhages during this stage are more dangerous than those that occur earlier in the disease. They are due to erosion of larger vessels which course in the walls between the cavities or to the rupture of small aneurisms that develop along those vessels. They may, therefore, be very profuse—sufficiently so at times to prove fatal.

The *fever* likewise assumes a different character, owing to the insinuation in the process of pyogenic bacilli, and is given an autonomous position in the symptomatology of the disease as *hectic fever*. It is, in fact, due to two distinct factors.* The first is protective. Pyogenic germs and their toxins are able to stimulate actively the adrenal center and thus to provoke high fever,* reaching generally 104° F. (40° C.), the highest point being reached daily late during the afternoon or in the evening. The temperature then falls, gradually, not to normal, as a rule, but considerably below, as low in some cases as 95° F. (35° C.), the minimum being attained during the early hours of the morning. The second factor does not always exist, viz., an artificial and supplementary fever similar to that evoked by tuberculin, and due to the additional heat energy liberated by the interaction of phosphorus derived from dead bacilli (which accumulate in enormous numbers during the third stage) and the excess of oxygen which the increase of adrenoxidase entails —this latter being due to the fever caused by the pyogenic germs. The temperature sometimes reaches 108° F. (42.2° C.) under these conditions. In the absence of mixed infection, however, or when the adrenal center is unable to respond to the stimulus,* the febrile process may be very slight or fail to occur.

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* *Author's conclusion.*

Sweating is also profuse in most cases, but in this stage it is due, during the presence of fever, to excessive congestion of the peripheral arterioles and to the resulting overactivity of sweat-glands;* but it may also occur as a result of depression, *i.e.*, during the afebrile period when the temperature is low and the pulse rapid and weak. *Diarrhœa,* due to a corresponding condition of the intestinal glandular elements,* is frequently present during the third stage and is an obstinate symptom.

Among the tardy phenomena are often observed patches of *pigmentation* varying from a yellowish tinge to typical bronzing. These indicate that the adrenal system is failing either through asphyxia of its center, owing to the drain of oxygen which the phosphorus of the disintegrated bacteria imposes upon the body at large, or on account of the excess of work of which the hectic fever is the expression.* Again, the adrenals and the thyroid are themselves the seat of tuberculous lesions in some cases; the typical symptoms of Addison's disease, including the bronzing, may then appear.

The physical signs are clearly defined. There is marked restriction of the respiratory movements of the chest. The *dullness* on percussion persists as long as areas of consolidation are present, but gradually, as cavities are being formed, the resonance increases until it assumes the tympanic character over the cavities. When large cavities are present, the *"cracked-pot" resonance* can be obtained (the patient's mouth being open) provided they are situated not too far from the point percussed. Palpation makes it possible in some cases to distinguish the areas of consolidation from the cavities, the *vocal fremitus* being much more marked over the former, owing to their superior sound-conducting power. Auscultation, when the caseous masses are liquefied, elicits *subcrepitant râles,* and if the air, on deep inspiration, passes through one or more cavities more or less filled with fluid, to reach other parts of the lung, *gurgling* or *bubbling* sounds may be heard. The bubbles formed by the air-streams often break and produce a sound resembling *metallic tinkling.* In cavities in which the air merely passes over the fluid, *cavernous* or *tubular breathing* is easily discernible; and if the air-current traverses the edge of a cavity, the *amphoric* breathing may be obtained—a sound resembling that produced when blowing across the mouth of a bottle. *Pectoriloquy* is a valuable sign to determine the location and size of cavities, when they are near the surface, the speaking or whispering voice being readily transmitted through them. All these signs are best obtained when the chest and back are bare, a light fabric, a handkerchief, for instance, being alone interposed between the examiner's ear and the patient.

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* *Author's conclusion.*

Finally the patient reaches the last stages of marasmus. Certain signs are apt to appear when the end is approaching, viz., *thrush*-like areas in the mouth and soft palate, which are in reality patches of tissue that are no longer the seat of active metabolism; *purpura*, due to breaking down of the cutaneous capillaries, and other manifestations of inhibited nutrition.* The disappearance of suffering incident upon this fact causes the patient during the last days of his illness to expect an early recovery, and some pass away cherishing this hope.

The wide fluctuations of fever are especially met in children. Thus Adams[64] states that in some the temperature may reach 108° F. (42.2° C.) and drop in a few hours to 95° F. (35° C.) without apparent effect upon the child. He has seen children eating the evening meal with relish, in spite of a rectal temperature of 106° F. to 107° F. (41.1° C. to 41.6° C.). Strümpell[65] places the average hectic fever fluctuation from 101.3° to 104° F. (38.5° C. to 40°C.). The rôle of pyogenic organisms in its production is generally recognized, and has been emphasized by Karl von Ruck.[66] This would seem to be antagonized by experiments *in vitro*, but Bernheim[67] has shown that the experimental (direct) antagonism between the tubercle bacillus and the pyogenic organisms does not prevail in the body and that the latter complicate the tuberculous process.

The presence of phosphates in the sputum of tuberculosis, especially when, as in the third stage, the tubercle bacilli are present in large quantities, has long been known, although the cause of this phenomenon has remained unexplained. Thus, C. J. B. Williams,[68] twenty years ago, stated, referring to the expectoration during the stage of excavation, that its pus contains "a large proportion of phosphates." Dubief, in Debove and Achard's treatise,[69] also says that the expectoration contains "phosphates in abundance." This may be due to the sodium phosphate of the blood or to the formation of this compound by the cellular nuclein, but it is not characteristic of other diseases in which the expectoration is profuse, catarrhal bronchitis, bronchorrhœa and kindred disorders, while it coincides with the results to be expected from the rapid proliferation of tubercle bacilli, the ashes of which show 60.9 per cent. of phosphorus (de Schweinitz).

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* *Author's conclusion.*

[64] Adams: Archives of Pediatrics, Dec., 1901.

[65] Strümpell: Münch. med. Woch., vol. xxxix, S. 905, 932, 1892.

[66] Karl von Ruck: New Orleans Med. and Surg. Jour., July, 1898.

[67] Bernheim: Indépendence médicale, Aug. 15, 1900.

[68] C. J. B. Williams: "Pulmonary Consumption," second edition, p. 93, 1887.

[69] Debove and Achard: "Maladies de l'appareil respiratoire," p. 363, 1896.

The failure of the adrenal system when the disease is advanced is shown by various stages of melanosis. Bronzing, varying from small melanodermic spots to large patches identical with those witnessed in Addison's disease, was found in 7 cases out of 24 by Laffitte and Moncany,[70] and in 12 cases out of 60 by Laignel-Lavastine[71]—all conditions such as freckles, friction stains, pytiriasis, lentigo, acanthosis nigricans, nævi, etc., being carefully eliminated. A similar pigmentation of the liver and spleen and other organs was reported by Weinburg,[72] in a case of tuberculosis. This observation recalls the finding of promiscuously distributed pigment, by Boinet,[73] in all of 20 rats in which he had caused lesions of the adrenals; the pigment had also permeated the subcutaneous cellular tissue, and proved to be identical with that found in Addison's disease. This applies likewise to the thyroid. Macaggi[74] found experimentally that in subacute and chronic tuberculous intoxication, the secretion of colloid was reduced and that the organ's epithelium became atrophied.

Etiology and Pathogenesis.—The predisposing cause of tuberculosis is a deficient functional activity of the adrenal system which may be inherited or acquired.* In the latter case, disease or hypofunction of either of the organs of the adrenal system (the thyroid, the anterior pituitary body, including the test-organ, the adreno-thyroid and the adrenals) may be caused by infectious diseases, starvation, overwork, insufficient oxygenation and other factors which either exhaust these organs by imposing excessive activity upon them, or greatly lower their nutrition.*

As Germain Sée says, "predisposition is a word employed to cover our ignorance"—an inevitable conclusion in the absence of an organ or set of organs whose mission is to govern the vital processes of the body at large—the rôle of the adrenal system. Indeed, the stigmata in such subjects clearly point to debilitated respiratory functions—both as to the lungs and tissues—the domain of this system. The flat, narrow chest and drooping shoulders, the winged scapulæ, obviously constitute an inefficient respiratory mechanism as illy nourished as is the rest of the slender figure; the pallor, the cold extremities, the sensitiveness to cold all point to inadequate oxygenation. It is this depravity of the adrenal system which alone, in my opinion, is inherited, and not the disease itself. This is quite in accord with the teachings of modern research; Senator[75] recently wrote, referring to tuberculosis: "In any event, a decisive rôle in determining the march and distribution of the scourge can never be attributed to hereditary predisposition."

The underlying cause of predisposition is disclosed, however, by the mutual relationship of certain diseases and the influence of hypofunction of one of the organs of the adrenal system, the thyroid gland, on infection.

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* *Author's conclusion.*

[70] Laffitte and Moncany: Bull. et mém. de la Soc. de méd. de l'hôp. de Paris, 3 série, vol. xx, p. 1228, 1903.

[71] Laignel-Lavastine: Arch. gén. de méd., Oct. 4, 1904.

[72] Weinburg: Rev. gén. de clin. et de thér., vol. x, p. 250, 1895:

[73] Boinet: Marseille médical, Apr. 15, 1896.

[74] Macaggi: Riforma medica, vol. xx, p. 873, 1904.

[75] Senator: Nothnagel's "Encyclo.," vol. on Tuberculosis, Amer. edition, 1904.

The predilection of chronic alcoholics to tuberculosis has been emphasized by Hector Mackenzie,[76] Lancereaux,[77] Monnier[78] and many others. Osler[79] holds that "chronic drinkers are much more liable to both acute and pulmonary tuberculosis." He believes that "it is probably altogether a question of altered tissue-soil, the alcohol lowering the vitality and enabling the bacilli more readily to develop and grow." Sims Woodhead,[80] Abbott and other bacteriologists have, in fact, demonstrated that alcohol predisposes to specific infectious diseases. Mays[81] and Kelynack[82] have shown that this applies as well to the tubercle bacillus. Among the cases reported by the last-named observer were 10 of alcoholic neuritis, 8 of which were subjects of pulmonary tuberculosis. As I have shown, alcohol reduces the adrenoxidase of the blood-stream and correspondingly inhibits the blood's vitalizing properties. The functional activity of the adrenal center being impaired as well as that of all other organs, it fails to respond actively to the stimulating influence of the bacterial toxins, and therefore to protect the organism adequately. That such is the case is shown by the fact that when the thyroid, whose secretion, as I have shown,[83] upholds the activity of the adrenal center, is itself hypoactive, as in myxœdema, a marked predisposition exists. Thus, as stated by Lorand,[84] "in myxœdema (athyroidea) tuberculosis appears frequently," as shown by Greenfield[85] and Byrom Bramwell;[86] "while," according to Pell,[87] "tuberculosis is very frequent in families of myxœdematous persons."

The influence of such a condition of the adrenal system is shown by the readiness with which a patient succumbs to tuberculosis when syphilis, a disease whose debilitating influence is doubted by no one, precedes the tuberculous infection. Niemeyer long ago taught that "the greatest danger for a syphilitic was to become tuberculous." Landouzy likewise emphasized this fact by the statement: "The worst combination I know of is that of pulmonary tuberculosis with primary syphilis." Jacquinet,[88] who refers to these and other authorities, reported 8 cases in which the two diseases were present, in all of which death occurred very rapidly, one patient indeed dying a few weeks after the onset of the tuberculous process. As I interpret these results, the adrenal system, already semi-paralyzed by the syphilitic virus, promptly yields when another depressant is superadded. Herbert,[89] in fact, recognizes a certain analogy between the primary and secondary stages of tuberculosis on the one hand, and syphilis on the other. Lorand states, moreover, that "Perrando[90] has found degeneration of the thyroid in the fœtus from parents with cachectic disease, especially syphilis." Garnier[91] has also found that "the thyroid in hereditary syphilis is degenerated and contains no colloid substance." As I pointed out in the first volume, it is this identical substance which, owing to its iodothyrin, upholds the activity of the adrenal center of the anterior pituitary to its normal level, *i.e.*, physiological standard.

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[76] Hector Mackenzie: Brit. Med. Jour., Feb. 27, 1892.
[77] Lancereaux: Revue gén. de clin. et de thér., vol. x, p. 47, 1895.
[78] Monnier: Gaz. médicale de Nantes, Nov. 12, 1895.
[79] Osler: "Pract. of Med.," third edition, p. 252, 1898.
[80] Sims Woodhead: Brit. Med. Jour., July 13, 1901.
[81] Mays: "Pulmonary Consumption," p. 61, 1901.
[82] Kelynack: Edinburgh Med. Jour., Sept., 1901.
[83] *Cf.* vol. i, p. 145 and 165 *et seq.*
[84] Lorand: Trans. Pathol. Soc. of London, vol. lvii, p. 1, 1906.
[85] Greenfield: Cited by Ewald: Nothnagel's "Handbook," p. 159, 1904.
[86] Byrom Bramwell: *Ibid.*
[87] Pell: Volkmann's Sammlung klin. Vorträge (Inn. Med.), Nu. 36, S. 255, 1895.
[88] Jacquinet: Presse médicale, vol. ii, p. 211, 1895.
[89] Herbert: Med. News, Sept. 8, 1900.
[90] Perrando: "Sulla struttura della Teroide," 1900.
[91] Garnier: Thèse de Paris, 1899.

This applies to all agencies that are capable of debilitating the adrenal system: starvation, overwork, insufficient oxygenation, infectious diseases, etc. "It has been found by several authors," writes Lorand, "that animals whose thyroid has been extirpated easily fall victims to infective processes." The great part taken by the thyroid in infections is shown by the researches of Bayon, of Wurzburg, and de Quervain, which establish the fact that in all grave infectious diseases, the thyroid is in the condition termed by them "thyroiditis simplex" without any secretion. Roger and Garnier[63] had found previously to the former authors, "a hypersecretion of colloid in the thyroid in infectious diseases which after some time may be followed by exhaustion of the gland."

All this applies as well to the pituitary body. Garnier and Thaon,[64] in a systematic study of this organ in tuberculosis, based on 18 cases, found invariably areas of sclerosis in the parenchyma in chronic cases, "the gland appearing less active than normally." In a more recent study based on a larger number of cases, Thaon[65] confirmed these observations.

Exhaustion of the gland here means cessation of the stimulus upon which the adrenal center depends for the preservation of its sensitiveness to poisons that appear in the blood. If it fails to receive this stimulus owing to a corresponding defect in the parents, the "predisposition" to tuberculosis—or any other disease—is inherited; if the deficiency of stimulus occurs as a result of diseases which have exhausted the thyroid or caused lesions either in the test-organ or in the posterior pituitary, the seat of the adrenal center, or in the adrenals themselves, we have the "acquired" predisposition. In whichever direction we scrutinise the question, therefore, we are ultimately brought to the conclusion that the predisposing cause of tuberculosis is deficient functional activity of the adrenal system.

In predisposed subjects the fluids of the body at large, including the secretions of the mucous membranes of the respiratory and digestive tracts, are deficient in auto-antitoxin and phagocytic leucocytes, the agents which under normal conditions destroy the tubercle bacilli and other germs that gain access to these fluids.* When tubercle bacilli are inhaled, the body's first line of defense, the anterior nasal cavities are not provided with mucus adequately supplied with these bacteriolytic agents. As these pathogenic germs can, under such circumstances, penetrate the nasal mucosa itself and enter the lymphatic system, infection may occur irrespective of any contamination through the lungs. It does not occur, however, if the adrenal system is fully active.*

The postulate of Koch that tuberculosis is caused by the inhalation of dried sputum, which met its conclusive proof in the studies of Cornet, has stood the test of time, though his opinion that this was the exclusive mode of infection has not. The manner in which dust may convey the disease may be illustrated by one of Cornet's more recent experiments.[96] Forty-eight guinea-pigs were placed in a room covered by an old carpet over which dried tubercular sputum mixed with dust had been spread, and the carpet was swept on four different occasions. The animals were killed after a time and 47 out of the 48 were found in an advanced state of tuberculosis of the lungs and bronchial glands. The same year (1888) that Cornet conducted his earlier experiments, Flick[97] showed that tuberculosis was especially prevalent in dwellings in which the disease had once occurred, 33 per cent of the infected houses having had more than one case and some houses showing eight deaths (in one instance, thirteen) in the course of 25 years, though in the great majority of instances different families had dwelt in them. The area of Philadelphia studied included about 50 blocks of houses.

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* *Author's conclusion.*

[63] Roger and Garnier: Presse médicale, vol. vi, p. 181, 1898.

[64] Garnier and Thaon: *Ibid.*, Oct. 11, 1905.

[65] Thaon: Thèse de Paris, 1907.

Yet in the human subject, Strauss[98] found purulent tubercle bacilli in the nasal secretions of 9 persons out of 29 examined, 6 of the 9 contaminated being hospital attendants. All were in excellent health. N. W. Jones[99] obtained 3 positive results from inoculations from 31 persons. Pollock[100] conducted a comprehensive study of the effects on the physicians and attendants of Brompton Hospital for Consumptives, covering a period of 34 years. It revealed no noticeable difference from the ratio of the disease among outsiders. There were no deaths from phthisis among the maids who swept and cleaned the floors several hours daily; of 101 nurses, 1 had phthisis in the hospital, 3 after leaving the hospital. Evidently the greater precautions taken in such institutions account partly for this showing, for in barracks, prisons, etc., the incidence of contamination is much larger. Still, why do not all soldiers, prisoners and particularly the hospital attendants whose nasal cavities contain virulent bacilli acquire the disease? It is here that the physiological efficiency of the adrenal system comes in: All functions are performed with adequate energy.

How is this auto-protective function carried on, on the surface of mucous membranes?

If, as I hold, the phosphorus in the tubercle bacillus is the real pathogenic agent, *two* modes of action should be discernible: one by the *living* bacteria, causing no particular local reaction, another by the *dead* germs, causing a local inflammatory reaction. Cornet[101] says: "When tubercle bacilli are gently rubbed into the nasal mucosa, no change occurs if care be taken not to injure the mucosa; in other cases, inflammation, reddening and ulceration shortly make their appearance." Since general infection occurs under these conditions, it can only be ascribed to *living* organisms absorbed, the local lesion being due to *dead* bacteria disintegrated during the procedure. That there is a solid foundation for this conclusion is shown by Cornet's statement[102] that "the dead forms exercise a more rapid and intense action, by means of the diffusion of their chemical matters, than do the live organisms with their slow process of proliferation." It is plain, however, that we cannot ascribe the resulting infection of the cervical and bronchial glands and of the lungs and spleen to which Cornet refers (especially the enormous multiplication of bacteria which this represents), to the chemical constituents of these organisms, which—interpreted from my viewpoint—caused the local inflammation, but to those which did not.

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[96] Cornet: Berl. klin. Woch., Bd. xxxv, S. 317, 1898.

[97] Flick: "The Contagiousness of Phthisis," Phila., 1888.

[98] Strauss: Münch. med. Woch., Bd. xli, S. 567, 1894.

[99] N. W. Jones: Med. Rec., Aug. 25, 1900.

[100] Pollock: Practitioner, June, 1898.

[101] Cornet: Nothnagel's "Encyclo.," vol. on Tuberculosis, Amer. edition, p. 101, 1904.

[102] Cornet: *Ibid.*, p. 119.

Indeed, that living tubercle bacilli can penetrate mucous membranes is well known.

The nasal mucous membrane affords considerable protection against infection. According to Wurtz and Lermoyez,[223] the nasal mucus is endowed with antiseptic properties, but researches by Park and Wright,[224] Liaras[225] and others did not substantiate this claim. H. L. Wagner,[226] however, found that, in accord with Buchner, Kossel and others, leucocytes produced a substance in the nasal secretions which possessed germ-destroying power. This substance, an enzyme, according to Wagner, does not necessarily kill the germs, but it diminishes their activity, and they are thus readily swept away by the secretions. This dual action prevents their penetration into the mucous membrane, and infection. The substance referred to is evidently the auto-antitoxin we have met everywhere. Piaget[227] found, moreover, that phagocytes took part in the process, while St. Clair Thomson and Hewlett[228] emphasized the fact that while the viscid mucus prevents the development of the bacilli, the ciliated epithelium promptly secures their expulsion. "The more active the secretion of mucus," writes Cornet, "and the more swift the current, the more rapidly is the bacillus eliminated."

When the tubercle bacilli reach beyond the anterior nasal cavities they are exposed to destruction by the bacteriolytic action of mucus and phagocytes of the pharyngeal tonsil in the naso-pharyngeal vault and the faucial tonsils. They penetrate the crypts of these organs and it is on reaching their epithelial layer to enter the underlying tissues that they are disintegrated. In predisposed, *i.e.*, debilitated subjects, the protective agents—the bacteriolytic phagocytes and endogenous antitoxin—are inefficient, and the tubercle bacilli being allowed to penetrate to the tonsillar lymphatics, infection occurs.

In some cases the quantity of tubercle bacilli destroyed in the pharyngeal and faucial tonsils is so great that the dead bacilli, owing to the quantity of phosphorus liberated,* provoke local tuberculosis.

Behind the nasal cavities, *i.e.*, in the naso-pharynx and pharynx, the defensive mechanism is of another order. St. Clair Thomson,[229] in painstaking studies of the subject, collected 1427 reported cases of naso-pharyngeal adenoids in which the reporters, including Lermoyez, Gottstein, McBride, Moure, Pilliet, Cornil and other authorities had examined the growths microscopically. Histological evidences of a local tuberculous process were present in 75 instances, *i.e.*, in 5.2 per cent. In another series of 435 specimens examined by Gouro, Broca, Hugh Walsham and Jonathan Wright, referred to by St. Clair Thomson, no evidence of local tuberculosis was found. This reduces the average to

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* *Author's conclusion.*

[223] Wurtz and Lermoyez: C. r. de la Soc. de biol., 9 série, vol. v, p. 756, 1893.

[224] Park and Wright: Cited by Wagner: N. Y. Med. Jour., Oct. 15, 1898.

[225] Liaras: Thèse de Bordeaux, 1899.

[226] H. L. Wagner: *Loc. cit.*

[227] Piaget: Thèse de Paris, 1896.

[228] St. Clair Thomson and Hewlett: Medico-Chir. Trans., vol. lxxviii, p. 239, 1895.

[229] St. Clair Thomson: Practitioner, Jan., 1896, and July, 1901.

4 per cent., but it does not disprove the fact that these growths are *penetrated* by bacilli. Indeed, Milligan and Dieulafoy found that 18.2 per cent. of adenoids were capable of causing infection when inoculated into animals, while Brieger found histological lesions in 5 out of 78 cases, and obtained one positive inoculation, though no tubercle bacilli could be found either on the surface or in the crypts. This appears paradoxical, but it is readily explained when the numerous phagocytes which such growths contain are taken into account. The successful inoculations are due to the presence of living, *i.e.*, undigested, tubercle bacilli derived from these protective cells, and the lesions—interpreted from my standpoint—to the phosphorus of the dead bacilli. This suggests that infection through the adenoid tissue of the pharyngeal vault is prevented by phagocytes. That such is the case is shown by the rôle of these cells in the tonsils, which are structurally similar. Recent investigations indicate, moreover, that in these lymphoid tissues, the endogenous antitoxin exercises its bacteriolytic action as everywhere else in the organism.

Goodale[110] found experimentally that foreign substances were ingested by polynuclear leucocytes in and adjoining the tonsillar mucous membrane, and that while bacteria are found in the crypts they are absent beyond the mucous layer, thus suggesting that "at the moment of entering," the bacteria "encounter conditions which terminate their existence." Kayser[111] also observed a defensive cellular process between the epithelial layers and the tonsillar tissues and that very little dust reached the trachea. Jonathan Wright[112] discerned an additional feature in the process, however: that pathogenic germs which penetrated the tonsillar crypts could exercise a property, recently defined by Pfeiffer, Bordet and others, viz., that of provoking in the tissues with which they come into contact, and by means of a constituent entering into their own composition or "endotoxin," the formation of a bacteriolysin of which they, the pathogenic bacteria, were themselves the victims. We have here, therefore, as elsewhere, not only phagocytic protection, but a fluid capable of disintegrating the tubercle bacilli.

If this dual protective process prevails in the posterior nasal, or pharyngeal, tonsil as well as in the faucial tonsils, the disintegration of the tubercle bacilli should, at least sometimes, provoke local tuberculosis. Dieulafoy[113] considers that "primary tuberculosis of the pharyngeal tonsil occurs with about double the frequency of that of the faucial tonsils." Cases of primary tuberculosis of the latter have been reported by Schlenker,[114] Kruckmann, Schreibner,[115] Orth,[116] Stewart,[117] and many others. The tonsils are also frequently involved in pulmonary tuberculosis.

The protective rôle carried on by these lymphoid organs is illustrated by the fact that Latham,[118] by inoculating into animals the central portions of hypertrophied tonsils, removed from 45 otherwise normal children, obtained 7 positive results. Again, in 19 instances out of an aggregate of 161 cases, adenoid vegetations, removed from otherwise healthy children by Lermoyez,[119] Gottstein,[120] Brindel,[121] and Pluder and Fischer,[128] provoked tuberculosis in animals, the children had all lived with tuberculous parents.

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[110] Goodale: Archiv f. Laryn., Bd. vii, S. 90, 1897.
[111] Kayser: Jour. of Laryn., Apr., 1898.
[112] Jonathan Wright: Med. News, Mar. 4, 1905.
[113] Dieulafoy: Cited by St. Clair Thomson: *Loc. cit.*
[114] Schlenker: Wien. med. Blätter, Bd. xvi, S. 630, 1893.
[115] Schreibner: Deut. med. Woch., Bd. xxv, S. 343, 1899.
[116] Orth: Cited by Cornet: *Loc. cit.*
[117] Stewart: Brit. Med. Jour., May 4, 1895.
[118] Latham: Lancet, Dec. 22, 1900.
[119] Lermoyez: Annales des mal. de l'oreille, etc., vol. xx, p. 979, 1894.
[120] Gottstein: Berl. klin. Woch., Bd. xxxiii, S. 689, 714, 1896.
[121] Brindel: Rev. hebd. de laryn., vol. xvi, pp. 881, 912, 1896.

When the nose alone is used in breathing, the air, on reaching the larynx, is practically free of bacteria; breathing through the mouth, however, deprives the larynx of the protection afforded by the nasal passages and tuberculosis of the larynx may be engendered by tubercle bacilli inhaled with the dust. This occurs very rarely, however. The organ is protected, when foreign substances reach it, as are the anterior nasal cavities, by a copious supply of mucus derived mainly from the ventricles of Morgagni, the secretion being directed outward, *i.e.*, towards the œsophagus. In almost all cases, however, tuberculosis of the larynx occurs as a complication of pulmonary tuberculosis.

Whether primary or secondary, the initial cause of tuberculosis of the larynx is deficient nutrition of its tissues which exists throughout the entire organism, owing to depravity of the adrenal system.* The fluids, lymph, blood and secretions of these tissues being deficient in bacteriolytic activity, the tubercle bacilli not only penetrate the lining epithelium, but being met therein by phagocytes inefficient themselves as bacteriolytic agents, they multiply in the laryngeal lymphatics and start a local tubercular process. The lesions caused by inhaled bacilli usually begin in the portions of the larynx most exposed to the inspiratory current, the tissues overlying the arytenoid cartilages and the posterior and upper surface of the epiglottis. When a laryngeal tuberculosis occurs as a complication of pulmonary tuberculosis, the tissues of the interarytenoid space, which extend over the arytenoid cartilages, are usually the first affected, the bacilli under these conditions being derived from the sputum, which the tracheal ciliated epithelium propels upward.

When voided from the larynx by coughing or hawking, the pulmonary discharges are either expectorated or swallowed, thus exposing, in the latter case, the gastro-intestinal tract to infection.

The pallor of the laryngeal tissues and of the adjoining tissues indicates that deficient nutrition prevails here as elsewhere. A curious feature of the treatment of laryngeal tuberculosis points in the same direction, viz., that irritation, mechanical or chemical, is beneficial: Thus the beneficial effects of lactic acid are greatly enhanced if, while applying it, the mucous membrane is rubbed. The hyperæmia produced with its attendant leucocytosis is obviously the main beneficial agent, the lactic acid aiding by destroying what bacilli it reaches.

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* *Author's conclusion.*

[128] Pluder and Fischer: Archiv f. Laryn., Bd. iv, S. 372, 1896.

Cases of primary tuberculosis of the larynx have been reported by E. Fraenkel, Trifiletti,[223] J. Solis Cohen[224] and many other observers since. In some of these instances careful examination of the lungs showed that they were normal. Such instances are rare in comparison to the laryngeal tuberculosis that accompanies pulmonary tuberculosis, and which occurs in about 35 per cent. of all cases. The opinion that infection by the sputum can occur is disputed by some, but as Cornet[225] says, "The theory of certain authors that laryngeal tuberculosis is not due to contact of the mucous membrane with the sputum, but is, as a rule, hematogenous in fact, lacks all foundation in fact."

The human gastric juice does not destroy tubercle bacilli ingested with contaminated milk, meats or other foods. When the germs reach the intestine, however, they are subjected to the proteolytic action of the auto-antitoxin in the succus entericus, before being ingested by the digestive leucocytes.* In vulnerable, *i.e.*, debilitated subjects, the succus entericus is insufficiently active to affect the virulence of the bacilli; they not only penetrate freely the intestinal epithelium to the lymphatics under these conditions, but they are ingested living by the digestive leucocytes.* The proteolytic activity of these cells being also impaired in vulnerable individuals, they are unable to digest all the bacilli ingested by them with food-stuffs in the intestinal canal, and thus distribute living tubercle bacilli germs throughout the entire body, including the lungs. General infection can thus occur, through the intestinal canal, from two directions: (1) direct penetration of the germs through the intestinal walls, (2) through the intermediary of the digestive leucocytes.*

Wesener[226] and others have contended that the gastric juice could destroy tubercle bacilli, but the investigations of Frank,[227] Fischer,[228] Straus and Wurtz,[229] and Cadéac and Bournay[230] have shown that such was not the case, while Lukaszewicz[231] suggested that the activity of the juice had some influence on the result, since the feeding of tuberculous meat from the one animal to dogs and cats would infect the latter, but not the former. The experiments of Carrière[232] showed conclusively, however, that human gastric juice sometimes attenuated the bacilli, but failed to kill them. Sabrazès had previously suggested that the greater part of the elements which constitute the tubercle bacillus were not, as in the case of cellulose and *nuclein*, susceptible to digestion. He found that it took 36 hours' immersion in gastric juice to deprive the germs of their vitality.

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* *Author's conclusion.*

[223] Trifiletti: Boll. d. mal. dell'Orecchio, etc., No. 5, 1887.

[224] J. Solis Cohen: Archives of Laryn., Apr., 1881.

[225] Cornet: *Loc. cit.*

[226] Wesener: Cited by Cornet: *Loc. cit.*

[227] Frank: Deut. med. Woch., Bd. x, S. 209, 1884.

[228] Fischer: Archiv f. exp. Path. u. Pharm., Bd. xx, S. 446, 1886.

[229] Straus and Wurtz: Arch. de méd. exp., vol. i, p. 370, 1889.

[230] Cadéac and Bournay: La province méd., T. viii, p. 284, 1893.

[231] Lukaszewicz: Thèse de St. Petersbourg, 1892.

[232] Carrière: C. r. de la Soc. de biol., vol. liii, p. 1098, 1901.

This accounts for the frequency of infection by way of the intestine, which, according to Macfadyen and MacConkey,[133] is more important in this particular as regards tuberculosis than the tonsils or adenoid growths. Klebs[134] considers it the chief avenue of infection, while Behring[135] has long held that in the young "the origin of epidemic pulmonary tuberculosis in man and the epizootic pulmonary tuberculosis in cattle, is through an intestinal route." A large number of cases in which fatal infection by milk had been clearly traced to tuberculous cows have been reported by Oliver,[136] Stang,[137] Demme,[138] Hills,[139] Ernst,[140] Stalker and Niles,[141] Leonhart,[142] Sontag,[143] Hermsdorf,[144] Rich,[145] Thorne,[146] all selected from literature with the greatest care by Professor Repp,[147] of the veterinary department of the Iowa State College, who holds with Theobald Smith,[148] Pearson[149] and Dinwiddie[150] and others, that the bovine tubercle bacillus is distinctly more virulent for the species of animals thus far experimented upon than is the human bacillus.

Having pointed out[151] that the intestinal food-products are taken up by the digestive leucocytes and converted by them into tissue elements, I held[152] that these cells were the normal agents of infection, and that when they failed to destroy the germ, living tubercle bacilli could be carried from the intestine to the lungs as well as to other organs. Sims Woodhead[153] says that: "When the tubercle bacillus is carried into the alimentary canal by the saliva, by food-stuffs, etc., it is rendered innocuous in more ways than one; but perhaps the most effectual way is by its being taken into the substance of *lymphocytes* which make their way out and in from the lymphoid patches, and which have the power of taking into their substance the tubercle bacilli. These lymphocytes return with their evil burden to the lymph-glands, and the glands assist in the complete destruction of the bacilli." Cornet[154] also says in this connection: "The bacillus has the power to penetrate not only the intact epithelium (Baumgarten, Dokroklouski, and Tschistowitsch), but also the entire wall of the gut, and to find its way along the lymph-channels to the mesenteric glands, where it first begins its actual career (Orth, Wesener and the author). This it accomplishes partly by mechanical means, partly by the aid of the *wandering cells*, and all without leaving behind a recognisable trace of its passage." Petruschky[illegible] was also led to conclude that it was through *leucocytes* that the bronchial glands were invaded.

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[133] Macfadyen and MacConkey: Brit. Med. Jour., July 18, 1903.
[134] Klebs: Congr. für innere Med., Bd. ii, S. 49, 1883.
[135] Behring: Trans. Tuber. Congr., Kassel, 1903.
[136] Oliver: Cited by Ostertag: "Hdb. d. Fleischbeschau."
[137] Stang: Cited by Law: Bull. Cornell Exp. Sta., No. 65, p. 137.
[138] Demme: Cited by Law: *Ibid.*
[139] Hills: Bull. Vt. Exp. Sta., No. 42, p. 55.
[140] Ernst: Rep. Mass. Soc. Prom. Agric., p. 4.
[141] Stalker and Niles: Bull. Ia. Exp. Sta., No. 20, p. 257.
[142] Leonhart: Cited by Watson: Rep. N. Y. Board of Health, 1892.
[143] Sontag: Cited by Watson: *Ibid.*
[144] Hermsdorf: Cited by Watson: *Ibid.*
[145] Rich: Vet. Mag., vol. iii, p. 729.
[146] Thorne: Ohio Vet. Exp. Sta. Bull., No. 108, p. 342.
[147] Repp: Phila. Med. Jour., Aug. 11, 1900.
[148] Theobald Smith: Trans. Assoc. Amer. Phys., vol. xi, p. 75, 1896.
[149] Pearson: Com. to Repp: *Loc. cit.*
[150] Dinwiddie: Bull. Arch. Exp. Sta., No. 57, p. 46.
[151] *Cf.* this volume, chapter fifteenth.
[152] Sajous: Monthly Cyclo. of Pract. Med., Jan., 1903.
[153] Sims Woodhead: Lancet, Oct. 27, 1894.
[154] Cornet: *Loc. cit.*

The importance of the intestinal auto-antitoxin in this connection is self-evident. In other words, the power of the intestinal juices to kill the tubercle bacilli (thus arresting their power to proliferate) is commensurate with the proportion of auto-antitoxin secreted into the intestine. As this depends upon the functional efficiency of the adrenal system, it is evident that hypofunction of this system predisposes the body at large to infection. Such a condition also involves general hyponutrition. As Sims Woodhead[illegible] says: "If the tissues be so weakened that their power of resistance can be readily overcome by comparatively few micro-organisms then infection will probably follow." This "power of resistance" means, from my standpoint, sufficiently active auto-antitoxin in all parts of the body to kill germs, *i.e.*, to paralyze their reproductive activity—the great initial danger in tuberculosis.

The lungs are mainly infected by tubercle bacilli which reach them, (1) with the air through the respiratory tract, (2) by phagocytes and lymph derived from the lymphatic supply of the naso-pharyngeal mucous membrane and lymphoid tissue, (3) by phagocytes and lymph derived from the lymphatic supply of the intestine.

(1) The entire bronchial tract is kept free of bacilli when the quantity inhaled is not excessive, by the ciliated epithelium which propels a current of mucus towards the trachea whence it is eliminated by way of the larynx. What organisms fail to come into contact with mucus of the epithelium (owing to their position in the middle of the air-stream) however, may reach not only the terminal bronchioles, but also the alveoli or air-cells which are not provided with ciliated epithelium. Here, they are met by phagocytes and auto-antitoxin, and if these bacteriolytic agents are sufficiently active,* the germs are promptly destroyed; if not,* the bacilli penetrate the alveolar septa, proliferate therein, and initiate the process of tubercle formation previously described.

(2) Infection of the lungs through the lymphatic system may be provoked by tubercle bacilli which have penetrated the epithelium of the nasal mucosa, or invaded the tissues proper of the pharyngeal or faucial tonsils owing to deficient bacteriolytic activity of the phagocytes of these organs. Once in the lymphatics adjoining the latter, the bacilli can proliferate freely since lymph is poor in all three of the constituents of

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* *Author's conclusion.*

[illegible] Petruschky: Münch. med. Woch., Bd. I, S. 364, 1902.

[illegible] Sims Woodhead: *Loc. cit.*

auto-antitoxin, and especially in adrenoxidase because of the absence of red corpuscles.* They invade in turn all the lymphatic glands of the neck down to the upper part of the thorax and thence the bronchial glands. As the lymph of these glands ultimately reaches the right and left lymphatic ducts to be poured into the subclavian veins, and thence into the superior vena cava and the right heart, it finally reaches all parts of the lungs. Having multiplied in an excellent culture-fluid, the lymph, the tubercle bacilli are thus transported by venous blood—in which they suffer no injury—to *all* the pulmonary alveoli.*

(3.) Infection of the lungs through lymphatic paths may also occur by tubercle bacilli derived from the intestinal canal, *i.e.*, with the leucocytes and fats that enter the lacteals and soon thereafter the thoracic duct. With the chyle of the latter these tubercle bacilli are also transported to the subclavian vein and thence to the superior vena cava and the right heart, whence they are distributed with the venous blood to all the pulmonary alveoli.*

The view that infection occurs through inhalation is the prevailing one and is urged by Cornet, who adduces the evidence afforded by the access of coal dust (in miners) and kindred substances to the alveoli themselves, though the coal-particles progressively decrease as these cavities are reached. "The ciliated epithelium, which is a powerful aid in removing foreign bodies, is absent in the alveoli," says this author, "so that these latter form a sort of storehouse for the dust particles"—and therefore, for what tubercle bacilli happen to be in the dust.

The opposite doctrine, that the bacilli reach the lungs through the lymphatics, has not gained support because it involved the conclusion that the germs and the phagocytes containing them had to travel against the lymph current from the bronchial glands to the pulmonary tissues,—a dubious proposition. By the *normal* paths I submit in the text, however, the lymphatic channels are not only in direct communication with the alveoli, but the germs or phagocytes containing them follow the direction of the streams to the latter, from begining to end, and land, unharmed, precisely where the tubercles are found, the external aspect of the alveolar walls, and the partitions between the alveolar recesses.

Viewed in this light, infection through the lymphatics, whether the bacilli enter the body by the respiratory or intestinal tracts, assumes a leading position in the pathogenesis of the disease. Cornet overlooks the fact that miners, stone-cutters, etc., work year after year in an atmosphere literally befogged with dust, and that under such conditions the penetration of particles to the alveoli is not surprising. A sound comparison could only be established if dust composed entirely of tubercle bacilli were also inhaled during correspondingly prolonged periods. The first condition is seldom if ever satisfied; the second, therefore, loses all weight. St. Clair Thomson[156] contends that "all our knowledge of physiology and all the laws of probability are opposed to the possibility of a germ successfully running the gauntlet of the intricacies of the upper air tract, the mucus spread out for it to adhere to, the phagocytes in readiness to slay it and the waving armies of ciliated epithelium in constant action to expel it." Nor are tubercle bacilli ubiquitous hosts of the respiratory tract as is the pneumococcus. Both Beco[157] and Boni[158] found that although the latter and many other organisms were present in normal lungs, the tubercle bacillus was never present. It must, therefore, be wafted directly from the external air to the alveoli to cause infection, without once coming into contact with bronchial walls which when the terminal bronchioles are reached are but three to four-tenths of a millimeter apart! It is self-evident that the number of germs that reach the alveoli directly under such conditions must be so small that even the local defenses of a weakling suffice to annihilate them.

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* *Author's conclusion.*

The lymphatic path from the naso-pharyngeal mucosa and the pharyngeal and faucial tonsils to the bronchial glands is familiar to every one. The path thence by way of the subclavian, the superior vena cava and the heart, to which I refer, is in accord with elementary anatomical knowledge. This applies likewise to the connection between the intestines and the thoracic duct. It remains to be shown, however, whether tubercle bacilli can occur in the lymph or chyle stream of the latter. This was demonstrated recently by Nicolas and Descos,[159] who found tubercle bacilli in the chyle of the thoracic duct after feeding dogs with soup to which they had added these germs.

Treatment.—The treatment of tuberculosis involves as a general principle the cardinal fact that the endotoxin of the specific pathogenic organism, Koch's bacillus, not only does not provoke (owing to its identity as a normal component part of the tissues, phosphorus) a reaction of the adrenal system, but that it contains also a poison which depresses the latter.* Its ravages proceed unchecked, unmolested, until a secondary infection, exciting the test-organ, counteracts the paresis produced by the tubercular poison and enforces, as it were, a reaction of the adrenal system—but too late, unfortunately, to arrest the lethal trend.* The indications are, therefore, to administer, at the earliest moment, *even though the diagnosis be uncertain,* agents which stimulate the test-organ, *i.e.*, the defensive properties of the adrenal system, with sufficient vigor to destroy the germ and its endotoxin.*

This applies of course only to cases in which, unlike the many instances referred to in the foregoing pages, spontaneous cure does not occur. In these instances (those in which evidence is afforded postmortem that tuberculous lesions have at some time existed) the curative process is essentially local, *i.e.*, similar to that following burns, injuries, etc., and irrespective of any intervention of the adrenal system.

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* *Author's conclusion.*

[156] St. Clair Thomson: *Loc. cit.*

[157] Beco: Arch. de méd., vol. xi, p. 317, 1899.

[158] Boni: Deut. Archiv f. klin. Med., Bd. lxix, S. 542, 1901.

[159] Nicolas and Descos: Jour. de physiol. et de path. gén., vol. iv, p. 910, 1902.

AGENTS WHICH CAUSE THE DESTRUCTION OF THE TUBERCLE BACILLUS AND ITS ENDOTOXIN.—The endotoxin of the tubercle bacillus, owing to the phosphorus it contains, supplies an active intermediary for the destruction of the germ itself when it penetrates the arterial blood, owing to the presence of adrenoxidase in the latter.* The affinity of phosphorus for oxygen being very marked, the germ is at once attacked in the blood-stream; its main endotoxin is converted either into phosphoric acid, a benign and eliminable product excreted in the urine; or, the sodium of the plasma aiding, into sodium phosphate.* Tubercle bacilli are not, therefore, found, as a rule, in the blood,* though a protective covering protects them to a certain extent even in this highly oxygenized medium.

Ample evidence to the effect that the tubercle bacillus is rich in nucleo-proteid—a body rich in phosphorus—has been submitted.

The tubercle bacillus is protected, according to Ehrlich, by a resisting cell-membrane which accounts for its resistance to stains. When the blood is poor in oxygen, as in pre-agonal states, or when the "vitality" is very low, as in some general infections, it can also appear in the blood, where it has been found by Wechselbaum, Meisels, Lustig, Rutimeyer, Sticker and others.[180] That they are present only temporarily, however, and only when they suddenly invade the blood in great numbers, has been emphasized by the searching investigations of Lipari and Lodato,[181] who found that the bacillus was in reality present at no stage of the disease in this fluid. Nor did they find it in the blood of animals in which tubercle bacilli had been injected intravenously. This applies likewise to the proliferation of these germs. Cornet,[182] in fact, states that "the tubercle bacillus is not a blood bacterium and does not grow in the blood." This attests also to a radical difference from *extra corpore* or shed blood which, as shown by Koch, is the best of culture media.

The fact that the tubercle bacillus is readily destroyed in the blood-stream proper accounts for its rapid proliferation in the lymphatics, especially in those of the respiratory or intestinal tracts, through which infection occurs, since the lymph contains no red corpuscles and but little adrenoxidase.*

In the treatment of the disease, therefore, an important indication besides destruction of the germs is to prevent their proliferation in lymphatic vessels and glands. These two ends are met by increasing the functional activity of the adrenal system, since the resulting increase of adrenoxidase in the blood by augmenting greatly its oxygenizing power causes (1) a direct destruction of the tissue bacilli that are not encapsulated (in tubercles) and hastens local repair; and (2) an increased production of auto-antitoxin, which, owing to the accompanying leucocytosis, augments the phagocytic activity not only of the blood, but of the lymphatic system.*

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* *Author's conclusion.*

[180] Sticker and others: Cited by Cornet: *Loc. cit.*

[181] Lipari and Lodato: La Tuberculosi, Bd. I, Hft. ii, 1898.

[182] Cornet: Nothnagel's "Encyclo.," vol. on Tuberculosis, 1904.

Iodine is an efficient agent in this connection. Not only does it actively stimulate the test-organ and through it cause an increase of adrenoxidase, auto-antitoxin, and thyroidase in the blood and promote leucocytosis (and therefore phagocytosis), but it likewise increases the vulnerability of the bacilli to the phagocytes of the blood and lymphatic system by increasing the sensitizing power of the plasma and lymph.* The patient should be given 5 grains (0.3 gm.) of *potassium iodide* immediately after meals, in a glassful of water. In some cases, this suffices to develop after a few days a slight febrile reaction, the temperature ranging between 100° and 102° F. (37.8° and 38.9° C.), with an increase of cough, freer expectoration—the sputa showing bacilli in some instances, although these were absent before—and greater distinctness of the physical signs. This indicates that the curative process has begun.* If these signs fail to appear the dose should be gradually increased by 2 grains (0.13 gm.) every other day until 10 grains (0.6 gm.) are reached. If at this time the reaction does not occur (which is seldom the case when no diagnostic error has been made) iodine should in addition be introduced either by inunction or subcutaneous injection, resorting to either of the methods indicated below.

If the remedy is not well borne, or if distinct progress is not made, more vigorous drugs, viz., thyroid extract or mercury, are indicated.*

Joseph Walsh,[illegible] of the Phipps Institute, states that "the only specific which has stood the test of time in tuberculosis is iodine." The power of this halogen to increase general metabolism has been reviewed at length under "Iodine," to which the reader is referred. That it affects pulmonary morbid processes is emphasized by the fact that in dogs, injections of iodine have been found to increase markedly the bronchial secretion. Indeed, Sticker and subsequently Vetlesen[illegible] found that small doses of potassium iodide (one tablespoonful of 1½ per cent. solution, *t.i.d.*) caused the appearance of râles strictly limited to the pulmonary areas where tubercular lesions were likely to appear After two or three days the cough is somewhat increased and the expec

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* *Author's conclusion.*

[illegible] Joseph Walsh: The Georgia Practician, June, 1905.

[illegible] Vetlesen: Norsk Mag. f. Laeger, Oct., 1897.

toration likewise. Out of 27 cases, the 7 that were clearly tubercular gave these signs; while the 20 which failed to react in the same way (and to the tuberculin test likewise) proved not to be tubercular. E. F. Wells[185] *confirmed these observations and obtained the reaction in two-thirds of his cases.*

The use of iodoform in surgical tuberculosis suggested that it might also be of value in phthisis. Flick,[186] *after using this drug and europhen in a large number of cases, concluded: (1) That incipient cases can almost always be cured by europhen or iodoform inunctions. (2) That cases advanced to the breaking down stage may be improved very much by this method of treatment and can sometimes be cured.* A tablespoonful of the following mixture is rubbed into the inside of the thighs and arms before retiring at night: ℞ Europhen, 1 drachm (4 gm.); oil of rose, 1 drop; oil of anise, 1 drachm (4 gm.); olive oil, 2½ ounces (75 gm.). Bathing the regions treated with bay-rum on rising eliminates all odor. Iodoform has also been recommended by Daremberg, Ransom, DeRenzi, Knopf, Foxwell, Russell and others. Flick, however, prefers europhen.

Illustrating more pointedly the effects I attribute to the action of iodine upon the adrenal system, however, is a paper by Geo. A. Brown[187] who employed a solution composed of precipitated iodoform (96 per cent. I.) 100 grains (6.6 gm.); 125 minims (7.7 c.c.) of glycerin; carbolic acid 5 minims (0.3 c.c.); boiled distilled water 300 minims (20 c.c.). This solution is sterilized and injected after cleansing the skin and freezing it with ethyl chloride. In pulmonary cases 24 minims (1.4 c.c.) were injected at intervals varying from two to four weeks, or more toward the end, but with ¼ gr. (0.016 gm.) every four hours during the interval and inhalations of iodine. The improvement began from the first dose in all of the 14 cases reported, including cases of glandular, cutaneous and intestinal tuberculosis. The author states that *leucocytosis* is produced, that "the increase corresponds with the iodoform injected," and that it occurs *with a rise of temperature.* In a chart he also shows a marked *rise of urea excretion, which corresponds* with an *increase of appetite,* and *gain of flesh* and *strength.* The curative process in a cutaneous tubercle is described as follows: "There is a rise of temperature in the first twelve hours, and by twenty-four hours one notices a yellow spot in the center of the tubercle, and almost complete depletion of the inflammatory products in the skin around the tubercle. The skin becomes soft and pliable. By the end of four days the yellow spot becomes a crust, is absorbed or falls out and leaves a small ulcer, which soon heals over and eventually bleaches out as scar tissue."

Iodine is now preferred by most clinicians. It was highly recommended by Potain, Durante and other European authorities, and in this country by Ingraham, Knapp, Fleisberg and others. Among the more efficacious methods, those of Mellor Tyson, of Croftan may be mentioned.

T. Mellor Tyson[188] has used, in a large number of cases, at the Rush Hospital, an iodole composed of 20 grains (1.3 gm.) of iodine to the ounce of olive oil, one drachm (4 gms.) of which was rubbed into the skin three times a day, the dose being gradually increased to one-half ounce *t.i.d.* The patients also received 1/25 grain (0.0026 gm.) strychnine *t.i.d.*, nourishing food and were out-of-doors considerably. In the advanced cases the improvement was only temporary, but in the incipient ones it continued as long as the patients were under observation. The improvement covered general conditions, strength, weight, cough, expectoration, dyspnœa, appetite, and even physical signs. In some of the incipient cases the cough and expectoration disappeared entirely, while in others they diminished gradually; the greatest change in the physical signs was a diminution in intensity in the abnormal breathing sounds. The previously harsh bronchial or broncho-vesicular sound became soft and the expiratory sound seemed to be less marked. Râles that were heard over the affected area seemed to be markedly diminished and in some cases to disappear altogether.

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[185] E. F. Wells: Jour. Amer. Med. Assoc., Feb. 4, 1899.
[186] Flick: *Ibid.*, July 31, 1897.
[187] Geo. A. Brown: Montreal Med. Jour., Apr., 1906.
[188] T. Mellor Tyson: Jour. of Tuberculosis, Jan., 1901.

As Croftan[169] states, accurate dosage is essential, as large doses aggravate while too small doses prove inefficient. In a report of 27 selected cases, 19 of which had circumscribed areas of infection, treated by means of iodipin injections and which gave results "sufficiently striking to warrant an optimistic view"—though not conclusive—profuse sweats, some pyrexia, acceleration of the pulse; hypochondria were observed in some instances. Beginning with one drop of iodipin dissolved in one-half drachm (2 c.c.) of sterilized oil, one drop was added to the dose each day, the dosage being regulated by the effect. As soon as improvement became apparent the dose was continued 30 to 60 days. If insufficient it was increased drop by drop, not exceeding 60 minims (4 c.c.). Croftan regards incipient tuberculosis one of the most easily cured of bacterial diseases. See also page 27 in Vol. I.

Certain cases, those in which there is marked pallor of the mucous membranes, especially of the soft palate above the uvula, patients with auburn hair, or in a word, cases in which the vital process is markedly hypoactive, are rapidly benefited by *thyroid extract* in 1-grain (0.06 gm.) doses after meals, gradually increased to 1½ grains (0.1 gm.).[*] Such doses increase the general nutrition, and activate the defensive process more vigorously than the preparations of iodine.[*] Thyroid extract is also indicated when iodine or the iodides are not well borne by the patient.[*]

The treatment of tuberculosis by thyroid extract was employed first by myself. In the dose mentioned in the text its use has never given rise to untoward effects. In incipient cases, in which the physical signs are clearly marked, the benefit is sometimes obtained very rapidly. In one of my cases, a tall man weighing 170 pounds, the loss of weight, 45 pounds in eight months, was at once checked, and in three weeks he had regained 10 pounds. He is now in perfect health and his cough has completely disappeared. Thyroid extract is quite as effective in tuberculosis of organs other than the lungs—provided the doses used be not too large. It is not indicated in the third stage.

Klebs[170] used thyroid extract to counteract the achylia gastrica of tuberculosis. Not only did it prove effective, but the author cites two cases in which "the weight increased markedly as a result of the thyroid." The evidence is all the stronger in that the author did not realize that he was benefiting the general disease proper. We have seen that Morin (1895) noted atrophy of the thyroid in a large proportion of consumptives—a fact which in itself accounts for the beneficial effects I have observed.

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[*] *Author's conclusion.*

[169] Croftan: Jour. Amer. Med. Assoc., Nov. 17, 1906.

[170] Klebs: Berl. klin. Woch., Bd. xxxvi, S. 1100, 1899.

Mercurials, we have seen, are powerful stimulants of the adrenal system, the efficacy in syphilis being due to this property.* *Calomel* has been considered by some quite as efficacious in tuberculosis as mercurials are in syphilis. Small tonic doses should alone be used and mercurialism be strictly avoided. The *biniodide of mercury*, $^1/_{16}$ grain (0.004 gm.) three times daily is a safer preparation than calomel in this connection and is equally effective.*

Stuart, Shattuck and Bowditch[171] coincide in the view that if every case of pulmonary tuberculosis were treated with mercury and potassium iodide more might be cured. Edelheit[172] obtained very favorable results from the use of calomel both in tuberculosis and bronchopneumonia and attributes his results mainly "to the property calomel possesses of stimulating organic changes and the vitality of all mucous membranes, including those of the respiratory tract." The beneficial results were especially marked in the chronic type, and much less so in acute and subacute cases. He administers it in pill form: ℞ Calomel, 0.6 gm. (10 grs.); beechwood creosote, 2 gms. (30 grs.); balsam tolu, 6 gms. (90 grs.); extract of calamus and powdered calamus, of each enough to make 60 pills, 6 of which are to be taken daily. Giampietro[173] also reported a number of cases cured by calomel, which he considers as much of a specific in tuberculosis as it is in syphilis. Other clinicians have found mercury of great value in tuberculosis. Miquel and Rueff,[174] Martell[175] and others who obtained favorable results by using it in the form of spray, ascribe the benefit to antisepsis; but sprays only reach bacteria that are being eliminated. It was the result—interpreted from my standpoint—of stimulation of the adrenal system after a sufficient quantity had been absorbed.

AGENTS WHICH ENHANCE THE NUTRITION AND THE PROTECTIVE EFFICIENCY OF THE LUNGS.—*Creosote* is a valuable remedy in the first and second stages of tuberculosis, excepting those cases in which the asthenia is to any degree marked.* In therapeutic doses it excites the test-organ, thus increasing the volume of auto-antitoxin in the blood, and simultaneously depresses the sympathetic centers.* The arterioles being dilated, an excess of blood rich in auto-antitoxin is admitted into all capillaries, including those of the diseased area, and the curative process is hastened.* The most satisfactory preparation is the *creosote carbonate*, which does not disturb the stomach even in large doses, when given during meals—half way between soup and dessert—and in capsules, which carry the drug safely, though it is a thick, oily liquid. Beginning with 5 drops three times a day, the dose can be increased gradually to 40 drops.

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* *Author's conclusion.*

[171] Bowditch: Boston Med. and Surg. Jour., Dec. [illegible], [illegible].

[172] Edelheit: Wiener Klinik, Bd. xxii, S. [illegible], [illegible].

[173] Giampietro: Gazz. degli Osped., vol. xvi, p. 1467, [illegible].

[174] Miquel and Rueff: Lancet, Nov. 3, [illegible].

[175] Martell: Wiener med. Woch., Bd. xxxix, S. [illegible], [illegible].

The beneficial effect of creosote carbonate is increased and any tendency to depress is counteracted by giving with each dose and in separate capsules, 2 grains (0.13 gm.) of *thyroid gland*.* The two agents can also be given to asthenic cases.* The addition of the thyroid gland, by increasing the proportion of thyroidase in the blood, also enhances its sensitizing action upon the bacteria (as opsonin)—a property which creosote only procures when given in very large doses.*

I showed in the section on creosote that it could markedly depress both the sympathetic and vasomotor centers. This, and the fact that the preparations available are not always pure, accounts for the cases in which untoward effects have been noted. Stoerk[176] taught that when it caused nausea or vomiting, it would do harm. This is an excellent guiding symptom, since it indicates gastric dilation and asthenia; but from my viewpoint this condition indicates that the use of creosote should be preceded for a time by a course of thyroid extract or iodine, to overcome the general asthenia. After two or three weeks the creosote is well borne. Since I have used creosote carbonate in the manner indicated above, even the largest dose mentioned has never caused the least gastric disturbance. Chaumier[177] gave from 10 to 20 gms. (150 to 300 minims) daily without causing the least gastric disturbance. The true contraindications are marked fever or tendency to repeated hæmoptysis.

The great rôle that creosote plays in the treatment of tuberculosis since it was first introduced by Bouchard, in 1877, needs no emphasis.

Strychnine causes effects somewhat similar to those of creosote, but through a different mechanism. It stimulates the test-organ and increases the proportion of auto-antitoxin in the blood; but it excites also the vasomotor center and by provoking constriction of all arteries, causes a larger volume of blood rich in auto-antitoxin to circulate in the capillaries, including those of the diseased area.* Beginning with $^1/_{120}$ grain (0.0005 gm.) three times daily, the dose is gradually increased until the physiological effects of the drug are noted, when the dose is no longer increased. Strychnine is now used mainly as a tonic along with other drugs, especially iodine. It should not be given with creosote, however, since it antagonizes its effects on the vascular centers.* *Adrenal gland* 3 grains (0.13 gm.) added to each dose of thyroid and creosote carbonate, in a capsule, may be employed instead.

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* *Author's conclusion.*

[176] Stoerk: Archiv f. Laryn. u. Rhin., Bd. I, S. 208, 1893-94.

[177] Chaumier: La médecine moderne, Nov. 16, 1895.

The value of strychnine in tuberculosis was pointed out by the late William Pepper,[178] who reported a case cured by this drug as main remedy. T. J. Mays[179] recommends it highly, and raises the dose from $^1/_{32}$ grain (0.002 gm.) very gradually until the physiological effects are observed (about $^1/_{12}$ gr.—0.005 gm.), then maintains it at that point. All symptoms are improved, including the cough. Ferran[180] likewise praises strychnine. W. F. Milroy,[181] who has used it considerably "with the most gratifying results," sustains Pepper's teaching that success "is dependent upon its administration in the maximum physiological dose."

Digitalis is highly beneficial in asthenic cases, especially when the heart is dilated owing to hypoactivity of the adrenal system.[*] Not only does it stimulate powerfully the adrenal center and greatly increase the quantity of auto-antitoxin in the blood, but the direct action of the increased adrenal secretion on the right ventricle, by augmenting the contractile power of the latter, causes the blood to be distributed with more vigor throughout both lungs, including the diseased areas.[*] *Digitaline,* ⅛ grain (0.008 gm.), gradually increased to ¼ grain (0.016 gm.) twice daily during meals if given alone, or one-half these doses if given with other adrenal stimulants, is of great value in the class of cases mentioned.[*]

In the first volume[182] I stated that "weakness of the right ventricle as a result of suprarenal insufficiency is an important factor in the pathogenesis," and also[183] that absolute integrity of the adrenal system is "a *sine qua non* of perfect immunity against pulmonary tuberculosis, *i.e.,* against the intrusion of pathogenic germs of any kind (and particularly the tubercle bacillus) in the circulations not only of the lungs, but also of the intestines." In a recent paper, Stow[184] adduced considerable evidence showing that "heart lesions accompanied by well-marked pulmonary stasis, thus concentrating in the lungs *the immunising agents of the blood, whatever they may be,* are rarely followed by phthisis pulmonalis, or if this previously existed, they exert a salutary effect upon it, and that the reverse conditions frequently are followed by pulmonary tuberculosis." The reader must be referred to the original for the data presented, which fully sustain what I have advanced several years earlier, pointing out also the identity and the source of the immunising agents. The digitalin I use in the class of cases mentioned is Merck's German, which is uniform in its action.

The influence of *high altitudes* on the prevention and cure of pulmonary tuberculosis is due to the concomitant action of some of the factors referred to above.[*] The atmospheric pressure being reduced proportionally with the altitude, the volume of oxygen per cubic foot of air is correspondingly reduced.

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[*] *Author's conclusion.*

[178] William Pepper: Univ. Med. Mag., Dec., 1895.

[179] T. J. Mays: Jour. Amer. Med. Assoc., Oct. 10, 1896.

[180] Ferran: La médecine moderne, vol. xii, p. 253, 1901.

[181] W. F. Milroy: N. Y. Med. Jour., Aug. 25, 1906.

[182] *Cf.* vol. i, p. 222, Foot-note.

[183] *Cf.* vol. i, p. 774.

[184] Stow: Amer. Jour. Med. Sci., Oct., 1906.

In order to insure adequate oxygenation, the number of red corpuscles is (physiologically) increased, and the proportion of oxyhæmoglobin (adrenoxidase) likewise. The contractions of the heart and vessels being more vigorous and numerous, more blood, richer in adrenoxidase,* circulates through the lungs in a given time than at a lower altitude. The conditions that exist under the influence of digitalis are thus reproduced, viz., the lungs are more actively immunized during health and disease.*

Out-of-door life, i.e., living in the open air as nearly as possible all the time, is a potent factor in the cure of tuberculosis. Sunlight and fresh air are themselves remedial, the latter by affording the adrenal secretion as it passes the alveoli to become converted into adrenoxidase,* a volume of oxygen which the partially reduced air of a room does not afford. The balcony, roof, or garden of a residence may be used to advantage in this connection, warm clothing and shelter from wind and rain being about the only precautions indicated. The breathing of cold air is not hurtful, day or night, as a given volume of cold air contains more oxygen than the same volume of warm air.

That the pulse-rate, the rate and depth of respirations and the vigor of the cardiac contractions are increased in high altitudes is generally recognized. The fact that the respiratory exchange is actually increased was shown by Bürgi.[155] The augmentation of red corpuscles corresponds with the altitude; thus Huggard,[156] in a table, gives among others the following comparative observations: Sea level, 4,074,000 (Laache); Zurich, 411 meters, 5,752,000 (Stierlin); Davos, 1560 meters, 6,551,000 (Kündig); Arosa, 1800 meters, 7,000,000 (Egger); Cordilleras, 4392 meters, 8,000,000 (Viault). Comparative experiments at Basle (266 meters) and Davos (1560 meters), by Jaquet and Suter,[157] showed, moreover, that in rabbits "the entire quantity of blood was greater by 14.8 per cent. in the Davos than in the Basle rabbits." Huggard also states that "the hæmoglobin usually increases in amount." De Saussure[158] observed in high altitudes "a kind of fever produced by the frequency of the respiration, which quickens the circulation of the blood."

Space cannot be devoted to a description of the many devices that have been proposed to insure adequate out-of-door life and yet protect the patient from the inclemencies of the weather. Considerable valuable information on the subject will be found in a recently-published work by J. B. Huber, of New York, on "Consumption and Civilization."

AGENTS WHICH CAUSE DESTRUCTION OF THE TUBERCLE BACILLI INDIRECTLY.—The beneficial effects of *tuberculin* are indirect in that this substance depresses the test-organ. It *provokes a fall* of the opsonic index which lasts from a few hours to two weeks. This is due to the depressing action it has upon the test-organ, which entails a corresponding decrease of adrenoxidase in the blood.* The general adynamia observed during the first and second stages indicates that tissue metabolism is deficient from the start, owing to this factor—the identical one which causes the opsonic index to be low in this disease.* When successive doses of tuberculin are administered, the blood becomes too poor in oxygen to carry on catabolism (the phase of metabolism always morbidly influenced first), and waste-products of various kinds, including the detritus from the diseased areas, accumulate in the blood.* A pseudo-pyæmia or septicæmia being thus evoked, the usual result follows: the adrenal system reacts more or less actively,* as shown by the rise of temperature. The blood becomes rich in auto-antitoxin; the opsonic index rises and the destruction of wastes and detritus proceeds—along with all the tubercle bacilli that are within reach of the blood's adrenoxidase, its thyroidase, and its phagocytes.

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* *Author's conclusion.*

[155] Bürgi: Arch. f. Anat. u. Phys., Physiol. Abth., S. 509, 1900.

[156] Huggard: "Handb. of Climatology," p. 127, 1906.

[157] Jaquet and Suter: Corres. f. schweitzer Aerzte, Bd. xxviii, S. 104, 1898.

[158] de Saussure: Cited by Huggard: *Loc. cit.*

Hence the danger of employing large doses of tuberculin. The functional activity of the test-organ and of all the organs of the adrenal system is lowered to such a degree, that the protective mechanism cannot react, and the more tuberculin is injected the worse this condition (the negative phase of Professor Wright) becomes. This entails another morbid factor: the proportion of auto-antitoxin and thyroidase in the blood being greatly diminished, the tubercle bacilli are allowed to multiply rapidly, the adrenal system is increasingly depressed, while the blood is further deprived of oxygen. A vicious circle is started which ends in general collapse.* The discouraging results obtained by Koch and his followers when tuberculin was first introduced are thus accounted for.

When minute doses of tuberculin are used in chronic cases which show a low opsonic index and no fever, such untoward effects do not occur. The blood's adrenoxidase is only reduced sufficiently to permit a slight accumulation of toxic wastes*—enough to cause a reaction of ½° to 1° F. (0.28° to 0.55° C.).

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* *Author's conclusion.*

As the least increase of auto-antitoxin in the blood is destructive to any tubercle bacillus reached, each time such a febrile state is brought about many germs are destroyed and the time finally comes, in suitable cases, when none remain to propagate their kind.*

This process accounts for the manner in which tuberculin indicates the presence of tuberculosis, *i.e.*, for its usefulness in *diagnosis.** In a normal subject the presence of an average quantity of adrenoxidase causes the tuberculin to be destroyed at once; conversely, a tuberculous subject whose test-organ (and therefore the adreno-thyroid centers) is already materially depressed is always on the verge of pseudo-pyæmia due to hypocatabolism.* The additional reduction of oxygen which the test-dose entails suffices, therefore, to produce the most prominent symptom of pyæmia: fever.*

All this is based upon the effects of Tuberculin T. R. employed by Professor Wright. The fact that this observer says himself that there occurs after its use "a period of intoxication which is characterized by a *decline* in the antibacterial properties of the blood" which is "more or less prolonged" according to the dose, shows plainly that its effects are due to direct stimulation of the test-organ. The character of the febrile process incited is plainly that described—a normal outcome of the depression which the tuberculin produces.

The various explanations of the mode of action of the many vaccines and sera tried so far, have included the word "immunity." Koch ascribes it to a local action on diseased areas; Ehrlich to union with receptors produced by tissue-cells; Marmorek to a sensitizing action on the tubercle bacilli, combined with a thermogenic action. Behring—at least his new T. C.—to a direct action on the cells of the host. These are in reality but guesses which throw no light upon the question. Wright's demonstration of the increased opsonic index has furnished the most valuable indication on this score, though even he does not point to the source of the immunizing substances. Indeed, without the adrenal system, which supplies all the factors required to elucidate the question as a whole, the problem was inscrutable.

As to the results of sanatorium cases treated with tuberculin, a table prepared recently by Fortescue-Brickdale,[129] gives a percentage of 88 per cent. cures in 863 cases. In this country, Pottenger[130] collected 611 cases with 64 per cent. of cures. Both these series, however, refer only to patients in the first stage. Von Ruck, of Asheville, N. C.,[131] who uses a watery filtered extract—far safer, therefore, than tuberculin—has obtained good results in the three stages when the disease existed in an uncomplicated form, viz., 94 per cent. in beginning phthisis (171 cases); 65.7 per cent. in more advanced cases (350 cases); and 27.3 in the "far advanced stages" (352 cases).

The crucial feature of the question, however, is the comparison of patients treated with tuberculin, with patients in which it was not used, although the climatic and other advantages were the same. Trudeau, of Saranac Lake,[350] gives the following percentages calculated on the basis of an equal number of treated and untreated patients:—

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* *Author's conclusion.*

[129] Fortescue-Brickdale: Bristol Med.-Chir. Jour., Mar., 1908.

[130] Pottenger: Therap. Gaz., Mar. 15, 1908.

[131] Von Ruck: Med. Record, Jan. 20, 1908.

TUBERCULIN—	INCIPIENT		
	Apparently cured	Disease arrested	Active
Treated	56 per cent.	34 per cent.	10 per cent.
Untreated	50 per cent.	38 per cent.	11 per cent.

TUBERCULIN—	ADVANCED		
	Apparently cured	Disease arrested	Active
Treated	27 per cent.	55 per cent.	18 per cent.
Untreated	6 per cent.	51 per cent.	43 per cent.

The post-discharge mortality affords more exact evidence, however: The following table includes the cases discharged during the last 15 years from Saranac Lake, omitting the last year:—

TUBERCULIN—	INCIPIENT		ADVANCED	
	Living	Dead	Living	Dead
Treated	79 per cent.	21 per cent.	61 per cent.	39 per cent.
Untreated	63 per cent.	37 per cent.	36 per cent.	64 per cent.

Although these figures do not show so striking a result as statistics based on all cases treated with tuberculin, the fact remains that tuberculin improves greatly the chances of recovery. One salient point asserts itself, however: the advanced cases are shown to derive considerable benefit from this treatment in sanatoria, a fact which cannot be said to apply to private practice. Conversely, judging from the results obtained by others and my own, I believe that during the first and second stages of the disease, the use of iodine, thyroid, etc., in the manner indicated, and with the auxiliary measures, saline solution, out-of-door life, etc., affords at least as good a chance of recovery as the use of tuberculin or any similar method of treatment.

Agents Which Increase the Alkalinity of the Blood.—Important in connection with all the foregoing measures is the preservation of the alkalinity of the blood up to its normal standard, a condition which tuberculosis tends greatly to compromise, thus decreasing in proportion the auto-protective functions of the body. The lymph circulation being rendered still more torpid than usual, the bacteria are retained longer in the lymphatic vessels and glands,* where they rapidly proliferate. When its osmotic properties are normal, the bacteria are swept with relative rapidity into the blood-stream, where they are soon destroyed.*

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* *Author's conclusion.*

[350] Trudeau: Amer. Jour. Med. Sci., Aug., 1903.

The patient should be urged to drink freely of water. When he eats normally, the addition of *sodium chloride,* 10 grains (0.6 gm.), to a glass of milk, taken twice daily, and the free use of vegetables to insure an extra supply of potassium salts to the blood, suffice.* In the more advanced stages, however, the measures recommended farther on (under "Fever") are indicated.

Stadelmann[153] and A. Robin[154] and many others have emphasized the importance of the loss of inorganic salts during tuberculosis. Even those who antagonize this view, Steinitz and Weigert,[155] admit that their chemical analyses showed a diminution of sodium and chlorine elements —both essential, we have seen, to osmosis. The addition of the salt solution—by enema or subcutaneous injection—in advanced cases is at times very beneficial. C. Rea Burr[156] characterizes as "extraordinary" the effect observed in one of his advanced cases. Quinton used injections of isotonic sea-water with success, a fact confirmed by Chauffard[157] and others. Carles[158] found the oral use of sea-water quite as effective. It does not cause the sudden rise of temperature—proof, by the way, that the auto-antitoxin is suddenly rendered able to carry on bacteriolysis, etc.—observed after its hypodermic use. The sea-water is simply filtered, since sterilization by heat impairs its virtues, and taken at first in spoonful doses half an hour before meals, the dose being gradually increased until half a tumblerful is taken. Watkins[159] observed "granules" or "third corpuscles" in the blood in tuberculosis—obviously blood-platelets, the presence of which, as I have shown, indicates deficient alkalinity.

SYMPTOMATIC TREATMENT.—*Cough.*—One of the most pernicious habits which the empirical administration of remedies has introduced is the use of opiates in the cough of tuberculosis. As they give relief by causing sympathetic constriction of the arterioles, they reduce the volume of blood admitted to the lesions and promote indirectly, therefore, the multiplication of the tubercle bacilli.* The retention of sputum which contains billions of these germs per cubic centimeter is obviously an additional source of danger. Cough is a protective phenomenon, and is due usually to excessive viscidity of the bronchial secretions—a baneful condition which is offset by the use of alkaline fluids, as stated above.* When the patient is undergoing the medicinal treatments indicated in the foregoing pages, especially *thyroid extract,* the *iodides,* or *creosote carbonate,* the cough soon shows signs of improvement, because the lesions themselves are being healed and the detritus ejected becomes gradually less.*

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* *Author's conclusion.*

[153] Stadelmann: Bull. gén. de thérap., Oct. 23, 1896.

[154] A. Robin: *Loc. cit.*

[155] Steinitz and Weigert: Deut. med. Woch., Bd. xxx, S. 838, 1904.

[156] C. Rea Burr: Boston Med. and Surg. Jour., Feb., 1906.

[157] Chauffard: Bull. méd., June 7, 1905.

[158] Carles: Province méd., May 26, 1906.

[159] Watkins: Med. Record, July 14, 1894.

Where the patient requires assistance is on rising, owing to the accumulation of muco-purulent secretions in the respiratory tract during the night. If he can rid himself of these before leaving the bed, he is usually comfortable the rest of the day. To facilitate this he should first resort to posture, viz., lying on the side opposite to that of the affected, with his head hanging over the edge of the bed. The cough being aided by gravity, considerable sputum is thus gotten rid of—the first installment. He should then carefully wash out his mouth, and drink a glassful of hot water containing twenty drops of *aromatic spirits of ammonia.* This is soon followed by a general feeling of warmth and a desire to cough. The former position being resumed, the remaining muco-purulent materials —those in which bacteria are usually found—will be voided. After again washing his mouth and cleansing his teeth carefully, the patient can then take his breakfast without being disturbed by spells of coughing. The same procedure on retiring tends much to insure a good night's rest.

I can only give here the general principles of measures which considerable experience in such cases has shown me to be effective. The physician's ingenuity will suggest many others on similar lines. I *never* prescribe opiates in such cases, and ascribe the good results obtained partly to this fact. It is a very unfortunate fact that the text-books still advise the use of such remedies, hydrocyanic acid, etc. The blind use of such agents and the fact that most cases of tuberculosis are dubbed "bronchitis" at first, thus giving ample time to the bacillus to do its fell work, is, in my opinion, one of the chief causes of the great mortality of tuberculosis—a disease which in its incipiency can almost invariably be cured.

It is important in this connection to distinguish between useful and useless cough. Some patients acquire the *habit of coughing,* and the least prickling sensation in the larynx is the signal for an artificial paroxysm which they could readily prevent if warned that it does harm. Indeed, examination of the larynx in such cases shows marked congestion, especially of the interarytenoid space. When this is present, *vomiting* is apt to occur, owing to the intense sensitiveness which the upper respiratory tract finally acquires. The instruction to the patient should be to avoid coughing until he feels distinctly that there is some mucus to eliminate. In some instances, he is unable to do this, and remedies are necessary to break the habit. After clearing the respiratory tract before retiring, as stated in a foregoing paragraph, *bromide of sodium*, 10 grains (0.6 gm.), may be taken, but only two or three nights. The laryngeal vessels, thus depleted (since the bromides in small doses depress the blood-pressure only) a few times, cease to congest the sensory terminals of the region.[*] Obstinate coughs are also benefited by the *oil of sandalwood*, 5 grains (0.3 gm.) three times a day, or fluid extract of *hydrastis canadensis*, twenty drops in water immediately after a meal. These substances are stimulants and aid the curative process. At times, however, they are not well borne by the stomach; *eucalyptus oil* 1 drachm (4 gms.) in *chloroform* 1 ounce (30 gms.), used as an inhalant, may then be tried.

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* *Author's conclusion.*

As already stated, the cough usually ceases to be troublesome after the general treatment recommended has had time to stimulate the diseased areas. When either iodine, the iodides or thyroid extract is used, the muco-purulent expectoration not only becomes free and is voided without difficulty, but the relaxation of the laryngeal vessels to which the local irritation is due, is overcome by the fact that their muscular elements are the seat of enhanced metabolic activity. The caliber of the arterioles being reduced, the laryngeal capillaries receive less blood.

Hæmoptysis is another symptom which is to a material degree prevented by the use, as curative remedies, of the preparations of iodine or thyroid extract, since by stimulating the adrenal system, they greatly increase the proportion of adrenoxidase in the blood.[*] As this body is the fibrin ferment the patient is supplied at all times with the ideal blood-constituent that will protect him.[*] Even hæmophilics are protected, since their blood under the influence of thyroid extract in small doses, becomes coagulable in less than three minutes, as compared to eleven minutes when untreated.[*] As in most instances the bleeding is due to ruptured capillaries, the presence of considerable fibrin ferment in the blood causes them at once to be obstructed by a coagulum, thus arresting the flow; the hæmorrhage is cut short almost as soon as begun.[*]

W. J. Taylor,[***] acting on my discovery that the adrenoxidase of the blood was the fibrin ferment and that thyroid extract, by increasing the production of the former, would arrest the bleeding even in hæmophilia, administered it in 3-grain doses (0.2 gm.) thrice daily, in three surgical cases. The coagulation time was reduced from eleven and one-half minutes to two minutes and six seconds in the most severe case, and the operation, entailing incision in the right loin and replacement of a kidney, was free from hæmorrhage. "To the astonishment of all present," says the operator, "the wound was remarkably dry, there being much less oozing than is usually seen in such operations." The effect was as striking in the other two instances.

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[*] *Author's conclusion.*

[***] W. J. Taylor: Monthly Cyclo. of Pract. Med., July, 1905.

When a free hæmorrhage occurs, the treatment of the tuberculous process must be set aside. As the purpose is to contract the arterioles, *morphine*, not less than 1/4 grain (0.016 gm.), hypodermically, is of great value, since it produces precisely this effect—provided atropine be not given simultaneously as is usually done, since this drug increases the propulsive action of the arterioles.* To prevent recurrence, *veratrum viride*, 5 drops (1905 U. S. P.), may also be given every hour three times, then every three hours. By causing a fall of the blood-pressure, it perpetuates the effect of the morphine. *Potassium bromide*, 15 grains (1 gm.), renewed in three hours, then in four hours, produces a similar effect,* and reduces the tendency to cough besides. *Chloral hydrate* in similar doses acts in the same way.* Either of these remedies does not prevent the use of a second dose of morphine four hours or more after the first, if needed.

Several auxiliary measures are important. The patient should be placed in a *semi-recumbent position* to avoid the untoward effects of gravity which recumbency and the vigorous cardiac contractions that the upright position entails, involve. *Cold or iced compresses* to the nape of the neck, which cause reflex sympathetic constriction of the arterioles, and a *bandage* tightly wound around one or more of the limbs to interfere with the return of blood to the heart, are likewise useful. The patient should *avoid all movements* for a few hours at least, and be relieved of anxiety by reassuring words.

My observations in such cases have led me to conclude with Jaccoud that morphine is the most efficient remedy in hæmoptysis; and also with Jay,[531] Piassetsky,[532] Fraenkel,[533] and others, that ergot should not be used in hæmoptysis. As I have shown under "Ergot," it causes a primary rise of blood-pressure and only subsequently constriction of the arterioles, and even this only when large doses are given. The patient is thus forced to traverse a dangerous phase to be relieved, and again when the effect of the drug is passing off, thus exposing him to secondary hæmorrhage. The use of digitalis, emetics, etc., is also condemned by the first-named observers, and rightly, too, in my opinion. The effect of the ice-bag is so marked, that Rossbach observed laryngoscopically blanching of the tracheal mucous membrane under its influence. This measure is also recommended by S. Solis-Cohen,[illegible] who applies the ice-bag over the heart or over the seat of bleeding.

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* *Author's conclusion.*

[531] Jay: Mercredi médical, Sept. 11, 1895.

[532] Piassetsky: Bjenedelnaya (St. Petersburg), No. 50, 1895.

[533] Fraenkel: Münch. med. Woch., Bd. xlvi., S. 877, 1899.

The *fever* of the two first stages is a protective process* and therefore does not require medication. Under the influence of the iodides or thyroid extract, it may increase at first and coincide with free expectoration and perhaps the appearance of bacilli which had not been detected before. If it persists, however, a good plan is to add *creosote carbonate* to the iodine or thyroid, beginning with 5 grains (0.3 gm.), but raising the dose only to 15 grains (1 gm.) during meals. This hastens the antitoxic process and the pyrexia is soon reduced to a slight but salutary level.

The fever of the hectic stage is partly due to a cause which has so far escaped attention, viz., a marked rise of the blood-pressure, due to irritation of the vasomotor center by the great quantity of toxic wastes and detritus in the blood.* Large enemata of warm (110° F.—43.30° C.) *saline solution* once daily, after the bowels have been moved, or *hypodermoclysis* or even *endovenous* injections of the same solution, greatly improve the patient's condition by promoting osmosis* and a free flow of urine, which carries away large quantities of the noxious substances. He should also drink copiously of a beverage composed of *milk and Vichy* mineral water, equal parts. These measures afford considerable relief.

Antipyretics do more harm than good. This applies especially to the coal-tar products, the use of which, as emphasized by many observers, causes marked depression. Aspirin has been recommended, but it causes profuse and depressing sweating.

The *nightsweats* of the hectic period are closely allied to the febrile process. The peripheral congestion incident upon the general vasoconstriction plus the febrile process, *i.e.*, the supreme effort which the adrenal system is making to rid the body of the tubercle bacilli and their endotoxin, and also, at this stage, of those that constitute the "mixed infection," becomes such, periodically, that the sweat-glands are themselves excited to hyperactivity.* This is mainly due to the physiological function which supplies the skin with moisture, the evaporation of which cools the surface. The measures just described are of cardinal importance in this condition, therefore, since they tend to rid the blood of the poisonous substances which exaggerate the febrile process.* Sponging of the body is very helpful during the sweating, and medicines should be avoided at this stage.

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* *Author's conclusion.*

[illegible] S. Solis Cohen: Jour. Amer. Med. Assoc., Feb. 22, 1901.

The nightsweats of the first and second stages, and of the third stage when there is hypothermia, are due to the general depression of the adrenal system, which, as we have seen, the presence of the tubercle bacilli entails.* The peripheral arterioles being relaxed (as under the influence of pilocarpine) the sweat-glands—that is to say their spiral muscles—become passively congested and overactive* and free sweating occurs. The aim here is to restore the arterioles to their normal caliber.* *Atropine* fulfills this precise rôle, provided, however, it is not given in too large a dose; $^1/_{100}$ grain (0.00065 gm.) hypodermically, or $^1/_{60}$ grain (0.001 gm.) by the mouth, usually suffices. It is preferable to morphine, which constricts the arterioles unduly. Another agent which acts much as does atropine is *camphoric acid;* it may be given in two doses of 15 grains (1 gm.) each, at short intervals, in capsules or cachets, two or three hours before the sweating period begins.

I have never used camphoric acid, but Stockman[illegible] states that it is more effective than atropine and that the tendency to excessive sweating soon disappears.

General Hygiene.—The specified diets often prescribed may be reduced to the simple formula: three substantial meals daily. With out-of-door life and appropriate treatment based on full recognition by the physician of the functions of the adrenal system in the curative process, the chances of recovery are very great, at least in the first and second stages of the disease.* No patient should be allowed to lapse into the third stage.

Prophylaxis does not, of course, enter within the scope of this work, but I would urge that the very laudable and fruitful work done at the present time in this direction should include a recommendation to practitioners to attach more importance to "coughs and colds" than they do. Most of the cases that the consultant is called upon to examine are victims of carelessness in this direction. My own plan is to treat *all* coughs of obscure origin, especially those ascribed to "colds," as if I were dealing with incipient cases of tuberculosis, without, of course, mentioning the fact to the patient. I prescribe 10 minims (0.6 mg.) of *creosote carbonate* and $^1/_{40}$ grain (0.0016 gm.) of *strychnine*, or 1 grain (0.06 gm.) of *thyroid gland* instead of the strychnine, during each meal, and instruct the patient to remain out of doors as much as possible. A common cold or even a "bad cold" promptly disappears under this treatment without opiates or syrups—and the patient is fully protected in case the cough should prove to be, as is often the case, the first and only sign of a tuberculous infection.

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* *Author's conclusion.*

[illegible] Stockman: Edinburgh Med. Jour., Jan., 1897.

CHAPTER XXVIII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

THE ADRENAL SYSTEM IN THE INFECTIOUS DISEASES OF THE LUNGS (*Continued*).

While the mortality of pulmonary tuberculosis has decreased during the last forty years, that of pneumonia has steadily increased. During the year 1890 the proportion of fatal cases in 1000 deaths from all known causes, in the United States, was 90.61; during the census year 1900 the corresponding proportion was 106.1. The deaths reported in the registration area during 1890 per 100,000 of population were 186.9. In 1900 this proportion had reached 192. In 1860 the corresponding ratio was only 44; in 1870 it was 102.4, and in 1880, 125.8. During the last forty years, therefore, the mortality of pneumonia has increased almost three and one-half times. As the deaths from "consumption" for the census year 1900 aggregated 109,750, while those from pneumonia reached 105,971, the latter disease may be said to be rapidly assuming the leading position among the foes of humanity. Thomas Darlington,[1] Health Officer of New York City, states that the death-rate has risen steadily from 1.95 per 1000 in 1870, to 19.5 per 1000 in 1904, and that it now leads all other diseases as a cause of death in our country's metropolis.

Referring to this appalling mortality of pneumonia, an editorial writer[2] recently asked: "Is this dreadful waste of human life inevitable? or is it the direct result of the nihilistic teaching of authorities who are grounded in the doctrine of 'self-limited' disease, and doggedly refuse to listen to the assertions of others as acute in observation and as honest in purpose as themselves, who claim that medicine is not powerless in the face of this devastating disease, and that pneumonia has been, and often can be, cured without waiting for the crisis on the seventh or ninth day?"

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[1] Thomas Darlington: Proceedings of the Phila. County Med. Soc., Mar. 22, 1905.

[2] Editorial: Medical Record, Oct. 28, 1905.

Analyzed impartially, this doctrine has its *raison d'être* with the prevailing ignorance of the physiological action of drugs as the foundation of a so-called "rational therapeutics." As urged by Hobart A. Hare,[8] referring specifically to pneumonia: "These are cases which remind us of the extraordinary bacteriolytic power of the blood, and the remarkable methods by which nature combats disease, and which should make us hesitate before we drop into the cog-wheels of such delicate machinery, drugs which may, if wrongly given, disorder or break down this complex mechanism." Indeed, of all diseases, pneumonia is the one which would bear the least the misuse of drugs—of vasoconstrictors when the sluices bearing a stream of antitoxin to the germ-laden areas should be widely opened; of oxygen-robbing alcohol when the blood's oxygenizing power should be in every way increased; of cardiac depressants when the ventricular contractions should be sustained, etc.

The doctrine that "pneumonia is a self-limited disease" disappears with the adrenal system as a foundation for the pathogenesis and treatment of pneumonia, for it points clearly to the measures that are productive of good and affords a logical, tangible, unequivocal explanation of the beneficial effects produced. A suggestive fact asserts itself, however, in this connection, viz.: that the agents indicated are precisely those which clinical experience, untrammeled by the theory of self-limitation, has sustained—those identical remedies urged upon the profession by men who have asserted that "medicine is not powerless in the face of this devastating disease," and that it "has been and often can be cured without waiting for the crisis on the seventh or ninth day."

PNEUMONIA.

Synonyms.—*Lobar Pneumonia; Pneumonitis; Fibrinous Pneumonia; Croupous Pneumonia.*

Definition.—Pneumonia, an infectious disease characterized by toxæmia and inflammation of one or more pulmonary lobes, is due to the multiplication in the latter of the pneumococcus lanceolatus of Fraenkel and, less usually, of the bacillus pneumoniæ of Friedländer, when from any cause the auto-antitoxin and phagocytes in the fluids of the respiratory tract, which under normal conditions destroy these germs and their toxins, are deficient in quality or quantity.**

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[8] H. A. Hare: Proceedings of the Phila. County Med. Soc., Mar. 23, 1905.

Symptoms and Pathology.—The morbid process may involve but one lobe, or a part of it, or extend to other lobes, and even to the other lung, thus constituting in the latter case the rare form of "double pneumonia." The physical symptoms may thus be circumscribed or widely distributed.

The onset of pneumonia is occasionally preceded by headache, a slight cough, oppression and pain in the chest, and general malaise of a couple of days' duration, but as a rule it is abrupt, and is marked by a *severe chill* in adults and vomiting and convulsions in children. What fever may have been present rises rapidly, reaching 104° to 105° F. (40° to 40.5° C.) within a few hours, and remains high. The face is flushed and shows deep-red spots on the side of the affected lung, and the skin is dry and hot to the touch. The pulse is generally strong and full, varying between 100 and 120. Both the temperature and pulse are apt to be high in children. The capillaries, especially those of the surface, are flooded with blood.* In children it is the rush of blood to the skin which, by exciting the sensory end-organs therein, provokes reflex convulsions.*

The *chill* is due to a temporary depression of the functions of the vasomotor center by the toxins when the toxæmia reaches a certain limit. As this is followed by a general relaxation of all the arteries, the blood accumulates in the great central trunks, depleting the surface. The peripheral temperature being lowered, the cutaneous muscles are caused reflexly to contract and relax rapidly—the "chill." The physiological purpose of this phenomenon is to conserve heat, if possible, through enforced motion. That there is depletion of the peripheral capillaries was shown by Maragliano[4] plethysmographically, the volume of the arm being decreased during the rigor. Moreover, Geigel[5] found that the temperature fell at this time.

The connection between the reaction (the rush of blood to the periphery shown by the sudden rise of temperature) and the convulsions in children, may be illustrated by the fact, demonstrated by Poulsson,[6] that even strychnine convulsions can be prevented by anæsthetizing with cocaine a frog's skin, thus paralyzing the sensory end-organs. The convulsions are obviously reflex.

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* *Author's conclusion.*

** *Author's definition.*

[4] Maragliano: Zeit. f. klin. Med., Bd. xiv., S. 309, 1888.

[5] Geigel: Allbutt's "System of Med.," "Fever," vol. i, 1905.

[6] Poulsson: Arch. f. exp. Path. u. Pharm., Bd. xxvi, S. 22, 1889.

An early symptom is a sharp pain on the affected side. This is accompanied by a short, dry cough which necessarily increases the pain (due to involvement of the pleura) and is therefore suppressed. It is often absent in the aged. Simultaneously, the respirations are increased in frequency, ultimately reaching in some cases 60 and even more a minute.

The fever remains high until the crisis, unless the subject be debilitated through alcoholism, squalor, a previous disease, etc. The fluctuations correspond very nearly with those observed during health, though exaggerated at times, especially when nearing the crisis; the nocturnal remissions averaging in most cases slightly above 1° F. When the crisis is near at hand a marked rise, 106° F. (41.1° C.) and over, may occur. In debilitated subjects the temperature range is lower; when it is very low, *i.e.*, below 101° F. (38.4° C.), the chances of recovery are greatly reduced.

The febrile process is evidently a protective one, the purpose being to increase the bactericidal and antitoxic properties of the blood.[*] Not only is marked leucocytosis present in cases that end in recovery, but this hyperleucocytosis is not observed in most cases that terminate fatally. It is usually absent in greatly debilitated, very young, and aged subjects, which constitute a large proportion of the mortality lists.

Leucocytosis may be low, however, in mild cases, and also in cases attended with very great intoxication. In the latter, the test-organ, overwhelmed by the toxins, is unable to enhance sufficiently general metabolism, and, therefore, the functional activity of the leucocytogenic organs.[*] Here, however, the febrile process is likewise low, and the depression is commensurate with the intense intoxication present. While a high fever ranging between 103° and 105° F. (39.5° and 40.5° C.), therefore, indicates a marked intoxication, it also shows that the protective functions are actively combating it.[*] Conversely, when in a severe case the temperature remains low, the probability is that the toxins are steadily overcoming these functions.[*]

Norris,[7] in a series of 500 cases treated at the Pennsylvania Hospital, found that the greatest number of recoveries occurred among those in which the temperature ranged between 103° and 105° F. (39.5° and

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[*] *Author's conclusion.*

[7] Norris: Amer. Jour. Med. Sci., June, 1901.

40.5° C.), while the highest mortality occurred in cases in which it fluctuated between 99° and 101° F. (37.3° and 38.4° C.). Many other examples of this kind are available in literature. The influence of debility is well illustrated by the fact that while the average mortality of the 500 cases was 25 per cent., the 34 known to have been drunkards showed a mortality of 67 per cent. The protective rôle of leucocytes, not only as phagocytes, but as the source of antitoxic, *i.e.*, proteolytic ferments, has been shown.[8] That leucocytosis occurs in favorable cases—subject to the conditions outlined above—is now generally recognized. Thus Ewing,[9] thirteen years ago, concluded that in most cases of lobar pneumonia "there is a marked leucocytosis. This may be absent or inconsiderable" adds this histologist: "*(a)* in very mild cases; *(b)* in very severe cases in which the reaction of the system is slight. The degree of leucocytosis in pneumonia is proportional, on the average, to the extent of the local lesion, but it follows much more exactly the grade of systemic reaction to the poison generated." The many researches published since, including the works of Stiénon,[10] Demoor,[11] and others have confirmed these observations. Stengel's[12] conclusion that the leucocytosis is of the active polymorphonuclear variety, the actively amœboid corpuscles being increased in greater proportion than the other forms, also summarizes the teachings of more recent observations. All this is applicable to the croupous pneumonia of children. Heim[13] for example, also found an increase of leucocytes in this disease. Hypoleucocytosis invariably proved to be a serious prognostic sign, though not necessarily fatal. All the cases studied—nineteen—showed a great increase of polynuclear neutrophiles, with a relative decrease of lymphocytes.

The febrile process remains about the same from five to nine days. The cough, at first short, becomes harder. In the beginning also, ropy, viscid mucus is expectorated, owing to concomitant bronchitis, but the sputum soon becomes red or reddish-brown, "rusty" or "prune-juice" like, and may contain fibrinous coagula. If gangrenous tissue be present, it may be very fœtid. Herpes on the lips and nose are commonly observed. The urine is scanty, high-colored, and sometimes contains albumin. A characteristic feature of pneumonia is that the chlorides are reduced or absent. There is also great thirst when the fever is high. Jaundice is an early symptom in some cases. The tongue may be dry and leathery,—a fact which suggests absence of alkaline salts and fluids in the blood. In simple pneumonia constipation is usual, but diarrhœa is apt to occur in the more serious cases.

During the FIRST STAGE, which lasts no longer than twenty-four hours, the air penetrates to the alveoli; *palpation* elicits a slight increase of vocal fremitus; *percussion*, if anything, a slight increase of resonance soon replaced by dullness; and *auscultation*, a broncho-vesicular murmur, soon supplanted by the typical crepitant râle at the end of each inspiration.

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[8] *Cf.* vol. i, pp. 610 and 671 *et seq.*, in the first edition.
[9] Ewing: N. Y. Med. Jour., Dec. 16, 1892.
[10] Stiénon: Ann. de la Soc. des sci. méd. et nat. de Bruxelles, T. iv, p. 49, 1895.
[11] Demoor: Jour. de méd. de chir., et de pharm. de Brux., July 6, 1895.
[12] Stengel: Jour. Amer. Med. Assoc., Aug. 19, 1899.
[13] Heim: Arch. de méd. des enfants, vol. iv, p. 21, 1901.

The pathological changes are characteristic. The affected area becomes intensely congested, and the capillaries between the air-cells or alveoli, and which course in their direction, are greatly distended. They evidently pour their contents into the alveoli, for the latter and the terminal bronchioles are more or less filled with red and white corpuscles, epithelial cells, etc., and blood-plasma. The leucocytes found in large quantities at this time are transitional cells, *i.e.*, cells which are developing into adult granular leucocytes, and which, closely examined, are found to contain lymphocytes (broken-down leucocytes), red corpuscles, nuclear detritus, and bacteria.

We are dealing evidently with phagocytic cells which are antagonizing the intruder and ridding the air-cells and terminal bronchioles of detritus. Examined post-mortem at this stage, these cavities are found to contain a bloody or reddish exudation, containing, when the lung tissue is slightly compressed, air-bubbles. It is this exudate which, when voided by way of the bronchi, gives the viscid sputum its prune-juice, rusty aspect.

Ritchie[14] in a recent presidential address, said: "I think it will be well for us to keep a mind open for the possibility that part of the increased metabolism may be the expression of work done by cells actively engaged in operating on the invading bacteria. That this is all the more likely is indicated if we correlate the known facts regarding the *increased excretion of potassium and phosphorus* during fever with the increased activity which can be microscopically observed *in the colorless cells* of the blood which contain *these elements in abundance.*" The correlation between leucocytosis and the prognosis of the disease referred to above, indicates the importance of this function. The presence of transitional cells was demonstrated by several investigators. J. Pratt,[15] for example, in fifty autopsies, found that in all cases dying within the first three days "the alveoli contained large numbers of cells closely resembling the so-called transitional cells." In accord with Ehrlich's view that all leucocytes, excepting lymphocytes, are transitional cells which ultimately become granular, Pratt's text shows that the cells referred to were becoming such, since "they were surrounded by a rim of but slightly granular protoplasm," while the nucleus was "nearly as irregular as that of the polymorphonuclear leucocyte"—the typical granular cells, which ingest bacteria. Councilman,[16] in fact, observed that they were "frequently phagocytic."

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[14] Ritchie: Brit. Med. Jour., Sept. 10, 1904.

[15] J. Pratt: Johns Hopkins Hosp. Reports, vol. ix, p. 265, 1900.

[16] Councilman: Jour. Boston Soc. Med. Sci., vol. iii, p. [illegible], [illegible].

The signs of the SECOND STAGE, that of consolidation, or red hepatization, are clearly defined: The chest on the affected side hardly expands, while the other side does so with unusual vigor; abdominal breathing is also increased. *Palpation* elicits a marked vocal fremitus; *percussion*, a woody dullness posteriorly, and a clearer though dull note anteriorly and tympany over the normal adjoining areas—thus affording a means of estimating the limits of the area involved. *Auscultation* affords information as to the degree of engorgement: if the bronchi are permeable, moist râles, bronchial and tubular breathing are heard; such is not the case with choked tubes, however—another differential test, since the permeable areas can thus be located. Bronchophony, pectoriloquy, or egophony may also be discerned immediately above the hepatized area.

The consolidated area contains cells and detritus, as it did in the first stage, but now the leucocytes are found, post-mortem, merged in with a copious network of fibrin-threads. This means that during life they were surrounded by a fluid containing the three constituents—phosphorus-laden nucleo-proteid, oxygen-laden adrenoxidase and trypsin—which jointly digest as auto-antitoxin not only the bacteria, but also their toxins.* Indeed, the typical polymorphonuclear granular leucocytes and their granules are found in large numbers often within the first forty-eight hours and thereafter. Death at this time is thought to be due to excessive accumulation of all the elements enumerated, since the fibrin is found to fill the air-cells, the small bronchi, etc., but as stated above, this is in reality a post-mortem change and the dense supply of fibrin only serves to prove that every available space is filled with the protective substances.* Many of these features are clearly illustrated in the annexed plate.

As I have shown in the first volume of this work, the material found in the tissues and which causes them to be termed "fatty" is not such: it is composed of the three constituents referred to above which during life are in the liquid state—all internal secretions. The presence of a ferment in the blood-serum has been demonstrated recently by Delézenne and Pozerski,[17] and their results have been confirmed by Hedin.[18] The latter investigator states, among other facts, that "the serum of the ox contains a weak *proteolytic* enzyme, which acts in an *alkaline* medium." He closes his paper with the statement: "As to the origin of the enzyme, nothing can be stated at present. Yet it should be remembered that a similar enzyme has been found in the *leucocytes* of the spleen, and it therefore does not seem to be impossible that the serum protease should be derived from the leucocytes in the blood or in other organs, either by a destructive process, which might set the enzyme free or by an act of secretion," the latter referring doubtless to secretion by the leucocytes. That the cells which secrete the antitoxic and bactericidal bodies are present in this stage is shown by the statement of Pratt that in 50 autopsies the typical-cells, the polymorphonuclears "were the predominating cells in almost all the cases dying after the third day," and that "they often appeared in large numbers within the first forty-eight hours." The experiments of Rosenow[10] showed that "the higher the leucocytosis, the fewer the number of pneumococci in the circulating blood." In 7 cases with a leucocytosis ranging from 35,000 to 43,000, "the number of pneumococci which developed was very small indeed, varying from 0 to 25 per cubic centimeter of blood." As these germs are the source of the toxins, the importance of the protective process I describe is self-evident.

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* *Author's conclusion.*

[17] Delézenne and Pozerski: C. r. de la Soc. de biol., T. lv, pp. 327, 690, 692, 1903.

[18] Hedin: Jour. of Physiol., vol. xxx, p. 195, 1903.

When the THIRD STAGE, that of gray hepatization, progresses favorably, it becomes the stage of resolution, for the abnormal physical signs enumerated gradually disappear. The râles in the bronchi become coarse and moist; this is followed by broncho-vesicular breathing which ultimately disappears. Considerable dullness over the affected area, however, may be elicited in some cases long after recovery.

The onset of this stage in the lung is attended by a still greater influx of leucocytes and a marked decrease of the red cells and plasma. Hence the gray—and in old subjects the granite-like—appearance at this stage which contributes a large share to the mortality of the disease, owing to the interference with the respiratory process and the increased labor imposed upon the heart.

When it marks the onset of resolution, however, it is because the accumulated leucocytes embody the elements necessary for their own liquefaction, *i.e.*, their nuclein and trypsin. With the aid of the adrenoxidase in the red cells and plasma these leucocytes undergo a process of digestion, *i.e.*, conversion into a purulent liquid which is either expectorated or carried to the blood by way of the lymphatics for final conversion into products of elimination.* At this time large phagocytes are also found in the pulmonary mass of detritus, which ingest in the main the identical polymorphonuclear leucocytes which now constitute the only source of danger. These various steps are followed by the proliferation of new alveolar and bronchial epithelial cells, and finally by the reconstruction of the disintegrated areas.

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* *Author's conclusion.*

[10] Rosenow: Jour. of Infectious Dis., Mar., 1904; Jour. Amer. Med. Assoc., Mar. 18, 1905.

The actual presence of a substance—such as trypsin—capable of digesting not only bacteria and their toxins, but also the cellular elements themselves, is well shown by the investigations of Flexner[59] in a large number of lungs obtained at autopsy. Salkowsky having demonstrated in 1882 that ferments played a very important rôle in physiological as well as pathological conditions, Flexner found that this was applicable to pneumonia in that autolysis occurred both in the stage of red hepatization, though imperfectly, and in that of gray hepatization, in which it took place rapidly and perfectly.

The presence of the large phagocytic cells referred to is well shown by the following statement of Pratt's: "They were found in nearly every case (50). *Late* in the disease they were often present in enormous numbers." As to their contents, he writes: "Red corpuscles, lymphocytes, and plasma-cells were occasionally seen, but the most common inclusion was the *polymorphonuclear leucocyte*. Often only nuclear fragments or partially digested cells were found. They also contained bacteria."

The *crisis* may occur any time between the third day and the end of the second week, but in most cases it occurs between the fifth and the ninth day. When it is near at hand the sputum becomes purulent and more abundant, and is eliminated with comparative ease. This sign, combined with the pronounced fall of the temperature, the relative comfort, a refreshing sleep, and sometimes free perspiration which characterize the crisis, points to the latter as being the true crisis, in contradistinction to the pseudo-crisis sometimes observed. These temporary falls of temperature may occur quite early, and recur several times. As previously stated also, the true crisis is usually preceded by a more or less sudden rise of one or more degrees. The gradual fall to normal or slightly below takes from eight to twelve hours.

The crisis marks the time when the bacteria and their toxins have been overcome by the body's auto-protective elements, the phagocytic cells and the blood's antibodies. Important in this connection, however, is the accumulation of toxic wastes and worn-out leucocytes in the blood. Welch[60] found that the blood of a person convalescing from pneumonia, three or four days after the crisis, was rapidly fatal to rabbits. Rosenow[61] also concludes from his observations that "patients with excessively high leucocyte counts are apparently more prone to the development of empyema and other complications." These features are closely related to the treatment adopted, since the use of appropriate measures prevents the accumulation of these worn-out cells by facilitating their removal, destruction in the blood-stream, and elimination.

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[59] Flexner: Univ. of Penna. Med. Bull., vol. xvi, p. 185, 1903.
[60] Welch: Medical Record, May 14, 1892.
[61] Rosenow: Jour. Amer. Med. Assoc., Mar. 18, 1905.

Complications.—*Pleurisy* is probably present in all cases excepting those in which the central portion of the lung is alone consolidated. It is sufficiently intense sometimes to warrant the term pleuro-pneumonia. The onset of pleurisy is attended by a rise of temperature, a sharp local pain, and the friction sound; and if empyema follow, by a marked increase of the leucocytosis and obscuration of the typical auscultatory signs of pneumonia. *Endocarditis* is observed in about 1 per cent. of the cases and aggravates the prognosis, since it occurs usually in persons suffering from some valvular disorder. The pulse is usually rapid and weak, the fever irregular, and there is considerable weakness. Rough murmurs are usually discernible. *Embolism* may occur in various parts of the body: the right ventricle and the lungs especially, the brain (causing aphasia and sometimes hemiplegia), and, rarely, in the larger arteries peripheral venous thrombosis has also been observed. *Pericarditis* is not infrequently caused through extension, it is thought, of the pleuritic inflammation. Among other possible complications are *arthritis, parotitis, and peripheral neuritis, otitis media, metastatic ophthalmia, nephritis, stomatitis, hepatitis,* and *cholecystitis.*

When empyema develops, the patient's life depends upon its early discovery and appropriate treatment. In 860 cases of pneumonia studied by Hale White and Chaning Pearce at Guy's Hospital,[illegible] 26 developed pyæmia, *i.e.*, 3 per cent. They attach great importance to a localised painful area and to œdema of the chest-wall. The temperature falls when crises should occur, but remains around 100° F. (37.8° C.) or thereabouts, and after three or four days rises again, there being an evening exacerbation. Endocarditis is ascribed by Preble[illegible] to the pneumococcus in almost all cases. It is oftener on the left than on the right side, but the tricuspid and pulmonary valves are affected four times oftener than in ordinary endocarditis. Emboli occur in one-half of the cases. On the continent of Europe cardiac complications are evidently rare: von Brach[illegible] only found in a total of 5738 cases of pneumonia 0.2 per cent. of endocarditis and 0.5 per cent. of pericarditis.

Etiology and Pathogenesis.—The primary cause of pneumonia is a deficiency in the body at large and in the air-cells of the lungs, of the auto-protective elements, *i.e.*, phagocytic leucocytes and auto-antitoxin. This deficiency, in turn, is due either to general adynamia, or to a temporary lowering through various external agencies of the temperature of the mucous membrane of the bronchi and alveoli.*

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* *Author's conclusion.*

[illegible] Hale White and Chaning Pearce: Lancet, Nov. 18, 1899.

[illegible] Preble: Amer. Jour. Med. Sci., Nov., 1904.

[illegible] von Brach: Cited by Schatzky: Roussky Vratch, Oct. 4, 1902.

The first of these factors, *general adynamia*, is brought on by conditions now known to impair the so-called "vitality," *i.e.*, debilitating diseases, deficiency of food, alcoholism, overwork, confinement in overpopulated quarters, such as workhouses, prisons, tenements, etc., where aëration is defective and sunlight scarce.

Cities furnish the largest proportion of deaths. In a single workhouse at Middlesborough, England, Ballard[36] witnessed 43 cases. Rodman[37] observed 118 cases in a prison containing 735 inmates. Daly[38] treated successively four brothers, then their mother. The latter having succumbed, her mother, who had come to attend the burial, also acquired the disease and died. Equally suggestive examples of the contagiousness of the disease have been observed by Mosler,[39] A. Ross Matheson,[40] Hamilton,[41] Newsholme,[42] Kühn,[43] Zimmermann,[44] and Sokoloff.[45] The latter author concludes, after an analysis of 2360 cases, that pneumonia can be transmitted from patient to patient in hospital wards. By isolating the patients and disinfecting the wards previously occupied by them, Sokoloff obtained a marked reduction both of the number of cases and of the complications in those isolated. That infection can occur from contaminated quarters was further shown by Jaworski and Chrostowski,[46] who treated five cases in a house which had not been free from pneumonia since 1860.

There is a marked predisposition to pneumonia during the first five years of life. The large proportion of deaths in children under one year old is due to artificial feeding, the infant being thus deprived of the antitoxin which the mother's milk alone affords; in cow's milk, which is, of course, used some time after being drawn, the adrenoxidase is reduced by the nucleo-proteid, and the antitoxin is thus decomposed*. After the age of twenty years there is a steady increase of vulnerability until old age is reached, when, with increasing years, the death-rate is very large. This form, *senile pneumonia*, is due, from my viewpoint, to the fact that senile failure of adrenal functions predisposes aged individuals to pneumococcic infection.

This is illustrated in the table given below, prepared from the United States censuses for 1890 and 1900. It gives the proportion of deaths during each census year for the five periods of life mentioned therein per thousand cases of pneumonia:—

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* *Author's conclusion.*

[36] Ballard: Lancet, June 22, 18[illegible].

[37] Rodman: Amer. Jour. Med. Sci., Jan., 1878.

[38] Daly: Lancet, Nov. 12, 1881.

[39] Mosler: Deut. med. Woch., Bd. xv, S. 245, 274, 1889.

[40] A. Ross Matheson: Brooklyn Med. Jour., Apr., 18[illegible].

[41] Hamilton: Brit. Med. Jour., May 20, 18[illegible].

[42] Newsholme: Practitioner, Jan., 18[illegible].

[43] Kühn: Berl. klin. Woch., Bd. xxv, S. 337, 1888.

[44] Zimmermann: Corresp. f. schweizer Aerzte, Bd. xxii, S. [illegible], 1892.

[45] Sokoloff: Bolnitchnaja Gazeta Botkina, No. [illegible], 18[illegible].

[46] Jaworski and Chrostowski: Jour. Amer. Med. Assoc., Dec. 1, 1888.

PER 1000 CASES OF PNEUMONIA.

Census Year.	First 5 Years.	5 to 19.	20 to 39.	40 to 59.	60 and above.
1890	304.7	70.2	195.8	203.9	225.4
1900	382,6	59.1	147.6	171.5	239.2

The highest death-rate is thus shown to be borne by the two extremes of life. In both infants and the aged the infection is due to inadequate defensive activity, owing to absence of the maternal milk in the former and to senile ductless glands in the latter.

During middle life (between twenty and fifty-nine years) pneumonia occurs more frequently among males than females, owing to the greater exposure and hardships to which the former are exposed. From the fifth to the twentieth year, however, *i.e.*, during childhood and adolescence, and during old age, the opposite is the case. This is accounted for by the greater vulnerability of the weaker sex.

During the census year 1890, the excess over females during this period of life was 22 per cent., and in 1900, 20 per cent.; but in early infancy, *i.e.*, up to 5 years, the difference between sexes is insignificant. Thus in 1890 it was 0.04 per cent. in favor of the males, and in 1900, 0.03 per cent. in favor of the females. From the fifth to the twentieth year, however, which includes the periods of childhood and adolescence, a noteworthy feature asserts itself: The females preponderate during both census years: 20 per cent. during 1890 and 10 per cent. during 1900. After the sixtieth year the preponderance of females over males is striking: in 1890 it was 25 per cent. and in 1900, 39 per cent.

Traumatism of the chest, a contusion, fractured ribs, etc., may lead to pneumonia even without giving rise to a solution of continuity of the pulmonary tissue. This is due to the disturbing effect of concussion on the pulmonary cellular elements, and to the consequent weakening of the local defensive processes.*

This form of pneumonia has been termed by Litten[37] "*contusions pneumonie.*" Souques[38] studied 49 cases due to blows upon the chest without solution of continuity of the pulmonary parenchyma. He found a pleuro-pneumonia in the majority of cases, but the course of the pneumonia in all instances did not differ from that of cases usually ascribed to infection. He found pneumococci in the sputum of his cases. Mandillon,[39] Gauthier,[40] and others have found the pneumococcus in abscesses developed under such conditions. In a case, immediately following a fall upon the pavement, witnessed by Schild[41] the typical lesions of croupous pneumonia were present, though the injury of the thorax had been insufficient to be recognizable.

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* *Author's conclusion.*
[37] Litten: Zeit. f. klin. Med., Bd. v, S. 26, 1882.
[38] Souques: La presse médicale, T. vii, p. 109, 1900.
[39] Mandillon: Jour. de méd. de Bordeaux, vol. xxvi, p. [illegible], 1896.
[40] Gauthier: Lyon médical, T. xcv, p. [illegible], 1900.
[41] Schild: Münch. med. Woch., Bd. xlix, S. 1569, 1902.

Exposure to cold and dry air—not damp air as is generally taught—predisposes to the disease, but only where the pathogenic organisms are present in the respiratory tract.

Pneumonia is less frequently met with in rural districts than in cities. It is only exceptionally met with among sailors. Sallard[42] states that it was extremely rare among Napoleon's troops during the retreat from Moscow notwithstanding the extreme hardships experienced. In large centers, Paris, for instance, similar conditions give rise to dissimilar results, for hackmen contribute largely to the yearly contingent of victims. Under such conditions exposure to cold is a prominent factor. In 79 cases recorded by Chomel, cold is incriminated 14 times, while Grisolle found this cause to prevail in 45 of 205 cases. Dampness is thought to increase the morbid effect of cold air, but H. B. Baker[43] has shown conclusively that this belief is based upon an erroneous interpretation of the actual condition of the air when it is said to be cold and damp. Cold air can hold relatively little moisture because its molecules are close together; warm air, on the other hand, can accommodate considerable since its molecules are far apart. Indeed Guyot's tables[44] based on Regnault's experiments show that air at zero F. contains per cubic foot (absolute humidity) when saturated with pure vapor, ½ grain Troy; at 32 degrees it contains 2 grains; at 70 degrees, 8 grains; at 98 degrees, 18.69 grains. It is cold, dry air, therefore, which lowers the resistance of the body to infection.

Ether-pneumonia is due to a similar condition.* The anæsthetic, owing to its rapid evaporation from the bronchi and alveoli, lowers the temperature of the broncho-alveolar epithelium, and of their contents. As ferments are activated by heat, this lowering of the temperature inhibits the activity of the proteolytic ferment in the leucocytes and the auto-antitoxin in the juices of the air-cells and bronchioles, which, under normal conditions, destroy the pathogenic bacteria and their toxins.* The germs are thus allowed to increase and to cause the disease.

This exemplifies the action of inhaled, cold, dry air as well.

General adynamia proves pathogenic in the same way, though indirectly. Starvation, squalor, fatigue, etc., entail inadequate nutrition not only of the body at large, but also of the organs that constitute the adrenal system, including the pituitary body.* As a result less adrenoxidase and trypsin are formed, and fewer leucocytes are present in the blood.* Again, the epithelial lining of the alveoli and the fluids bathing them are inadequately supplied with its protective constituents, and infection occurs if the pathogenic bacteria present are those of

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* *Author's conclusion.*

[42] Sallard: "Manuel de médecine," Paris, 1896.

[43] H. B. Baker: Ann. Report of Mich. State Board of Health, [illegible].

[44] Guyot: Smithsonian Meteor. and Phys. Tables, p. 39 B., [illegible].

PNEUMOCOCCI AND PHAGOCYTOSIS IN LOBAR PNEUMONIA. (Mme. N. Schultz.)

pneumonia, and if their number is sufficiently great to escape what protective elements are present.

Metchnikoff, Bordet, Ehrlich, Morgenroth, Zimmermann, and others are in accord as to the fact that it is this substance which enables the complement (the trypsinlike agent in the blood) to destroy wornout blood-cells, bacteria, etc. The complement being endowed, according to Ehrlich, with digestive powers, the immune body brings it into contact with the pathogenic elements, and these are dissolved. It is as certain that leucocytes containing this trypsinlike ferment and capable of shedding their nucleoproteid granules are present in the alveoli. Finally, since it is here as I have shown that the adrenal secretion becomes converted into adrenoxidase, it is here that this substance must be endowed with its highest efficiency.

The *micrococcus* or *diplococcus lanceolatus* of Fränkel is generally considered as the specific organism. It has been found in all portions of the respiratory tract, and in healthy individuals in the mouth, nose, Eustachian tubes, and larynx, and may persist a long time in the saliva of persons who have suffered from the disease. These organisms, and others that may be present in the air inhaled, pullulate in the bronchial fluids and even in those of the alveoli when the local defenses are inadequate.

Andrew H. Smith[illegible] compares infection to a "process of germ-culture going on in a culture medium, each air-cell acting as a tiny test-tube, and filled with this culture medium." Pasteur and Netter have found the micrococcus lanceolatus in the buccal secretions of 20 per cent. of well persons and accept Grossmann's view[illegible] that the pathogenic micro-organisms of pneumonia are "drawn downward into the respiratory tract by aspiration during ether narcosis," the type, we have seen, of existing conditions provoked by a reduction of the temperature in the alveoli, however produced.

The *pneumococcus* of Friedländer is another organism thought capable of provoking pneumonia. It differs from the diplococcus lanceolatus in being single instead of in pairs, and in being oval instead of pointed at one end, *i.e.*, "lance"-shaped. In some cases it is the only bacillus found. When this bacillus penetrates the blood the case is greatly aggravated. It is also found in pure culture in the various organs which become the seat of complications. It is often present in connection with pyogenic organisms, especially the streptococcus. Hence the name "streptococcus pneumonia" given to some cases of the disease.

[illegible] A. H. Smith: Medical Record, Nov. 18, [illegible].
[illegible] Grossmann: Deut. med. Woch., Bd. xxi, [illegible], [illegible].

That cases in which the pneumococcus is found in the blood offer a very unfavorable prognosis was noted by Sello.[47] Of 12 out of 48 cases (selected from a series of 750) in which it was present, 10 died. Of the balance of his cases, 36 in which the pneumococcus was not found but 7 died. This was confirmed by Cole[48] after a study of the blood of 129 cases, and of the literature of the subject. "The organisms obtained from the more severe and fatal cases" were "either more numerous or more resistant to unfavorable conditions." Sachs[49] witnessed a case in which practically all organs were the seat of abscesses due to the organism. Instances in which it was found alone in the tissues and lungs, have been reported by Philippi,[50] Stühlern[51] and others. In a report of an epidemic at the Leavesden Asylum, Sinigar[52] emphasizes the virulence of this organism. Interpreted from my standpoint, the presence of any bacillus in the circulation means insufficiency of the adrenal system and a marked diminution of the blood's bactericidal properties. Indeed, Müller[53] observed experimentally "destruction of the bacteria by the juices of the lungs."

Treatment.—This may be divided into two general indications: (1) to enhance by appropriate remedies the protective activity of the blood's immunizing cells and fluids, and (2) to sustain the efficiency of the protective resources of the body by measures which are known to preserve the physiological fluidity and osmotic properties of the blood.

AGENTS WHICH ENHANCE THE ACTIVITY OF THE IMMUNIZING PROCESS.—The efficiency of the blood's bactericidal and antitoxic properties can be increased by the use of agents which enhance the functional activity of the adrenal system and simultaneously tend to inhibit the multiplication of bacteria in the lungs. In the *senile* form injections of adrenalin, 10 minims (0.6 gm.) in a syringeful of saline solution should be given every three hours, avoiding any vein—a life-saving measure.

Creosote carbonate, administered *early,* in the senile as well as in the various other types, is as nearly a specific in pneumonia as quinine is in malaria, provided sufficiently large doses, 10 to 15 grains (0.6 to 1.0 gm.) be given frequently enough, *i.e.,* every two or three hours. Besides causing the arterial blood to circulate with greater freedom through the diseased area, it promotes the production of auto-antitoxin, and thus enhances the destruction of the pathogenic germs and their toxins.*

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* *Author's conclusion.*

[47] Sello: Zeit. f. klin. Med., Bd. xxxvi, S. 112, 1899.

[48] Cole: Johns Hopkins Hosp. Bull., June, 1902.

[49] Sachs: Zeit. f. Heilk., Bd. xxiii, S. 284, 1902.

[50] Philippi: Münch. med. Woch., Bd. xlix, S. 1884, 1902.

[51] Stühlern: Cent. f. Bakt., Bd. xxxvi, S. 493, 1904.

[52] Sinigar: Lancet, Jan. 17, 1903.

[53] Müller: Deut. Archiv. f. klin. Med., Bd. lxxi, S. 513, 1901.

Creosote carbonate produces no gastric disorders, and although the urine is sometimes rendered smoky, it causes no renal or cystic disturbance, even when the above doses are increased two or three times. The accumulation of toxins which occurs under other treatments does not take place, owing to the *feeble resistance of the specific organism* of pneumonia and the influence of the remedy, and the crisis is often replaced by lysis. The fever may, in fact, disappear within forty-eight hours. It is usually given in a solution of glycerine and peppermint water, but, though an oily liquid, it may be readily given in capsules, followed by a mouthful of water. It must be continued some time after subsidence of the fever, to avoid recurrence.

The use of this agent in pneumonia was introduced by Cassoute of Marseilles in 1898, and it has grown to be regarded by many observers, including A. H. Smith[54] and W. H. Thomson,[55] as the most efficacious remedy at our disposal. In a series of 1130 cases treated by various practitioners and collected by I. L. Van Zandt[56] the mortality was only 5 per cent. In sixteen personal cases Van Zandt had no deaths. Tuttle and Carter[57] recently reported 600 cases treated by them in six years. It reduced their mortality from 22.8 to 7 per cent. Baldwin, of Rome,[58] who gives as much as 30 to 40 minims (2 to 2½ gm.) every three hours, had 18 consecutive cases without a death, while the prevailing type of the disease was fatal. Scott and Montgomery[59] had a mortality of 14.9 in 67 cases. But they gave it every four hours only, whereas the other observers named gave it oftener, *i.e.*, every 2 or 3 hours, thus sustaining the bactericidal action of the remedy. Equally good results are obtained in children as shown in the series of cases reported by Seifert,[60] Louis Fischer,[61] and several European observers. Conversely, C. F. Stokes of the Navy[62] gave creosote carbonate successfully in cases ranging from 25 to 74 years, the latter being a very severe case. Wilcox[63] treated 33 cases without a death—avoiding all other drugs. It has been highly recommended by J. B. Philips,[64] Burdett O'Connor,[65] Fletcher,[66] and others. Beverley Robinson[67] considers creosote vaporized in the patient's room valuable as a prophylactic.

Sodium salicylate has properties similar to creosote carbonate, and has given equally good results. By exciting the test-organ it provokes an increase of auto-antitoxin, including thyroidase, in the blood, and by exciting simultaneously the sympathetic center, causes the arterioles to propel the blood with increased vigor into the diseased area, thus enhancing markedly the bacteriolytic and antitoxic process.* But it often provokes excessive sweating, tinnitus aurium, severe headache, and sometimes hæmaturia. It is also contraindicated when cardiac lesions are present. Conversely, it reduces the pleuritic pain and the thirst causes defervescence by lysis and greatly reduces the severity of the disease. It may be given in 8 to 10-grain (0.5 to 0.66 gm.) doses, every two hours, to adults, when creosote carbonate is not obtainable.

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[54] A. H. Smith: Med. Rec., Mar. 15, 1902.
[55] W. H. Thomson: *Ibid.*, Feb. 1, 1902.
[56] I. L. Van Zandt, *Ibid.*, Oct. 18, 1902.
[57] Tuttle and Carter: Cited by A. H. Smith: Amer. Therap., Jan. 15, 1905.
[58] Baldwin: *Ibid.*
[59] Scott and Montgomery: Therap. Gaz., Dec. 15, 1903.
[60] Seifert: N. Y. Lancet, Dec., 1899.
[61] Louis Fischer: Archives of Pediatrics, Feb., 1903.
[62] C. F. Stokes: Brooklyn Med. Jour., Aug., 1900.
[63] Wilcox: Amer. Jour. Med. Sci., Sept., 1902.
[64] J. B. Philips: Carolina Med. Jour., Nov., 1906.
[65] Burdett O'Connor: Northwest Medicine, Feb., 1906.
[66] Fletcher: Canada Lancet, Feb., 1907.
[67] Beverley Robinson: Medical Record, Apr. 7, 1906.

Although Talamon and Lecorché[68] failed to hasten defervescence, DeBecker[69] found it exceptionally valuable in infantile pneumonia. Sebring[70] had only one death in 100 cases, some of which received the salicylate alone. It is also recommended by Sir Hermann Weber[71] and De-Becker. Pye Smith[72] limits its use to cases complicated with rheumatism. F. D. Reese[73] recently reported twenty-one cases of pneumonia with but two deaths, one of the fatal cases being a woman of 83 years.

Among other agents of this class which have been tried and abandoned are *creosote, carbolic acid, eucalyptol,* and *naphthol,* owing to the irritating action on the kidney.

Quinine likewise floods the diseased area with blood rich in auto-antitoxin.* But this result is not obtained with small doses, since these only excite the vasomotor center and raise the blood-pressure.* Large doses, however, increase powerfully the propulsive activity of the arterioles by exciting the sympathetic center, and simultaneously the adrenal center.* So far it acts much as does sodium salicylate. Quinine is endowed with an additional virtue, however: that of acting as a direct bactericidal agent, the pneumococcus offering but slight resistance to agents capable of acting as does quinine upon the plasmodium malariæ.*

Quinine in large doses may thus be effective in pneumonia because it causes the arterioles to flood the diseased area with blood rich in auto-antitoxin and an additional and powerful germicide.* Creosote carbonate (*vide supra*) however, is safer.

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* *Author's conclusion.*

[68] Talamon and Lecorché: "Thérapeutique Appliquée," Robin, 1896.

[69] DeBecker: Ann. de la Soc. de méd. d'Anvers, vol. lx, p. 65, 1898.

[70] Sebring: Medical Record, Apr. 22, 1899.

[71] Sir Hermann Weber: Practitioner, Feb., 1900.

[72] Pye-Smith: Medical Record, Apr. 21, 1900.

[73] F. D. Reese: Medical Record, Nov. 26, 1904.

Quinine has been used by a few European clinicians, some, Juergensen,[74] having given it in 5-gram (77 gr.) doses. Recently W. J. Galbraith, of Cananea, Mexico,[75] called attention to the great value of this mode of treatment, emphasizing, however, the need of very large doses—a view thoroughly sustained by the interpretation of its action I have submitted. His method is as follows: "First a warm bath, followed by a calomel or phosphate of soda purge. The first dose of quinine is given three hours later provided the stomach is not disturbed. If the temperature is 105° F. (40.5° C.) or over he gives from 60 to 70 grains (4 to 4.6 gm.) of quinine sulphate, followed in an hour by usually half the same dose. If the temperature ranges between 103° and 104° F. (39.5° and 40° C.), from 40 to 50 grains (2.6 to 3.3 gm.) are given as above. If a lower temperature is found, he gives 40 grains (2.6 gm.), his minimum initial dose. The use of the tincture of the chloride of iron is begun within three or four hours after the second dose of quinine, and in doses ranging from 10 to 15 minims (0.6 to 0.9 c.c.) at intervals of from two to six hours, depending on the condition of the pulse. In case the temperature rises to 101° or 102° F. (38.3° or 38.9° C.), after it has reached the normal or subnormal mark, he administers from 40 to 50 grains (2.6 to 3.3 gm.) of quinine at one dose and continues the iron in 15 minim (0.9 c.c.) doses every three or four hours. He protests against any compromise in the way of dividing the doses of either iron or quinine during the active pneumonic stage. If the stomach is rebellious it may usually be overcome by chloretone or pepsin and guaiacol. He dresses his patients with as light-weight clothing as possible and provides thorough ventilation and advises plenty of liquid nourishment." A number of physicians, Drs. Gustetter, Carpenter, Haney, Butzow and Dudley, all of Cananea,—where the mortality of pneumonia is exceedingly high owing to the atmospheric conditions and the altitude,—have confirmed his observations in their own practices. From 75 per cent. in a very large number of cases, Galbraith's mortality, for example, dropped down to 2 per cent. Gustetter[76] of the Marine Hospital Service in the same region, reduced his average mortality, 80 per cent., to no death in the 30 cases with the same treatment.

S. Solis-Cohen[77] advocates the use of the soluble double hydrochloride of quinine and urea in 50 per cent. solution by intramuscular injection, with fresh air. When the blood-pressure is low, he adds injections of cocaine hydrochloride solution or an extract of posterior pituitary. In cases of prolonged fever and delayed convalescence, he also uses pneumococcus or mixed vaccines.

An important feature connected with the treatment of pneumonia is the preservation of the normal osmotic properties of the body fluids.* If the blood is abnormally viscid, as is the case when its alkalinity is low, its bacteriolytic and antitoxic properties are so hampered that the beneficial effects of the remedies are greatly compromised.*

AGENTS WHICH PRESERVE THE EFFICIENCY OF THE PROTECTIVE RESOURCES.—*Blood Salts.*—This object is met by supplying

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* *Author's conclusion.*

[74] Juergensen: Ziemssen's "Cyclopædia," 1875; cited by von Mansfelde: Jour. Amer. Med. Assoc., Mar. 17, 1906.

[75] W. J. Galbraith: Jour. Amer. Med. Assoc., Feb. 10, 1906.

[76] Gustetter: *Ibid.*, Mar. 17, 1906.

[77] S. Solis-Cohen: New York Med. Journal, p. 290, Aug. 9, 1913.

to the blood the salts it requires in order to conserve its normal fluidity and its normal properties. By thus facilitating the circulation of blood in the tissues, including the lungs, the latter are not only supplied with the protective elements available to disintegrate the bacteria and their toxins, but the toxic and acid wastes are freely drained into the blood-stream and transformed into eliminable products.

The salts of the blood "have most important functions" recently wrote Howell,[79] "they maintain a normal composition and osmotic pressure in the liquids and tissues of the body." . . . "Moreover, these salts constitute an essential part of the composition of living matter." Jacques Loeb[80] also states that, "the sodium ions of the blood as well as of the sea-water, are essential for the maintenance of life-phenomena."

In the first volume I pointed out that in pneumonia a large amount of sodium chloride was consumed; that owing to restricted diet or anorexia, the patient received an inadequate supply, and that the vital and defensive functions being increasingly hampered, the chances of death were considerably increased.*

The reader is referred to the first volume[81] for the experimental evidence contributed by Metchnikoff, Behring and Nissen, Paul, von Fodor, Blumenthal and many others in support of this conclusion. Barlow[82] alluding to diminution of the blood's alkalinity during fever says: "The cause of this change is quite unknown . . . but whatever the true explanation may be, it is probable that the change is highly important for the organism, for it is an unfavorable sign in febrile disease, and it is known that diminished alkalinity of the blood goes hand in hand with increased susceptibility to infection."

In pneumonia the chlorides are soon diminished in the urine, then disappear entirely. Inasmuch as even moribund cases are sometimes saved by saline solution hypodermoclysis, the need of sodium chloride is self-evident, and if introduced into the blood *from the outset* of the fever as suggested by myself[83] and not late in the disease as now practiced, the blood's protective functions and its osmotic properties may be adequately sustained throughout the disease.

Beale many years ago showed that the chlorides disappear from the urine to accumulate in the lungs. Huchard also emphasized the importance of this symptom. Hutchison[84] found, on the other hand, that the chlorides were taken up by all fixed tissues. Roehrich and Wiki[55] observed that when the crisis occurs and a rapid favorable change takes place, the chlorides suddenly become very abundant; but if defervescence is by lysis the increase is proportionately gradual, the normal proportion being reached in three or four days. Failure to rapidly increase is an unfavorable sign. Henry, who first used hypodermoclysis in "desperately ill" cases[56] nevertheless saved eight out of ten of these cases. As similar results have been obtained by others when all other means had failed, the physiological aid given by the salt is unquestionable. Yet, being recommended in text-books only for desperate cases, it is now rarely employed. Ewart and Percival[57] for instance state that saline injections "were powerless to check the fatal course" in "the worst type of cases." How can it be otherwise when the whole body is overwhelmed with toxins?

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* *Author's conclusion.*

[79] Howell: "T. B. of Physiol.," p. 801, 1905.

[80] Jacques Loeb: "Studies in General Physiology," part ii, p. 556, University of Chicago, 1905.

[81] *Cf.* vol. i, pp. 778 *et seq.*

[82] Barlow: "General Pathology," second edition, p. 415, 1904.

[83] *Cf.* vol. i, p. 784, in the first two editions.

[84] Hutchinson: Jour. of Path. and Bact., vol. v, p. 406, 1898.

Hypodermoclysis and intravenous injections of saline solution involving the frequent use of a large hypodermic needle, thus giving pain and exposing the patient to abscesses, are not appropriate for repeated use. The *oral* use of saline solution in the manner and under the conditions indicated on page 1367 meets all therapeutic indications. Hypodermoclysis may be substituted when, in advanced cases, an immediate effect is required.

The oral use of saline solutions was introduced by J. B. Todd, of Syracuse, N. Y.[58] Inspired by my views, he employed it *early* in all his cases, with prompt and satisfactory results. For an adult he gives 10 grains (0.6 gm.) of sodium chloride and 5 grains (0.3 gm.) of potassium bicarbonate, dissolved in 8 ounces (250 gm.) of water. A teaspoonful of lemon juice added to this mixture thus transforms it into an effervescent beverage which is gratefully taken by the patient. This quantity may be given to febrile cases every two hours. The potassium bicarbonate antagonizes acidosis. J. Madison Taylor[59] obtained similar effects in the pneumonia of children. This corresponds with the results reached by predecessors who, though unaware of the influence of salt solution on the immunizing processes, employed injections early. Thus in all cases in children reported by Lemaire,[60] he found that "the blood-pressure was promptly raised, diuresis was increased, the whole organism, notably the nervous system, was powerfully stimulated, oxidation was enhanced, and all recovered." F. W. D'Evelyn,[61] H. F. Thompson[62] and others have also extolled the value of this measure in severe cases.

SENILE PNEUMONIA; HYPOADRENIA.—We have seen that cases in which leucocytosis fails to occur, either through general adynamia, alcoholism, or when, owing to a profound toxæmia, the toxins have caused adrenal insufficiency, the chances of recovery are greatly reduced.* A deficiency of adrenoxidase being the direct cause of the adynamia, agents capable of increasing the functional activity of the adrenals are indicated.*

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[55] Roehrich and Wiki: Revue médicale, June 20, 1900.
[56] Henry: Intern. Clinics, vol. iv, ninth series, p. 29, 1900.
[57] Ewart and Percival: Brit. Med. Jour., Sept. 29, 1900.
[58] J. B. Todd: N. Y. Med. Jour., May 20, 1905.
[59] J. Madison Taylor: N. Y. Med. Jour., Dec. 30, 1905; Medical Record, Jan. 13, 1906.
[60] Lemaire: Semaine médical, vol. xviii, p. 405, 1898.
[61] F. W. D'Evelyn: Medical Record, Dec. 30, 1905.
[62] H. F. Thompson: Medical News, Apr. 25, 1903.

Digitalis.—In asthenic cases (excepting senile pneumonia, see first volume, page 12), digitalis should be used besides the *alkaline beverage* and the *creosote carbonate or quinine. This agent satisfies several requirements: By powerfully stimulating the adrenals it strengthens the action of the heart and the proportion of auto-antitoxin in the blood.* As in asthenic cases, there is relaxation of the arteries, full therapeutic doses of digitalis— 8 to 12* minims (0.5 to 0.8 gm.) of the tincture, or digitalin, $\frac{1}{10}$ *to* $\frac{1}{6}$ grain (0.0065 to 0.01 gm.), are required three times daily to obtain adequate effects.

That digitalis provokes leucocytosis was shown by Naegeli-Akerblom[53] and Borini.[54] Von Jaksch[55] long ago emphasized the need of such an agent in pneumonia. Its action on the heart is familiar to everyone. All these properties plainly account for the remarkable results obtained by many clinicians since Traube in 1850 first suggested its use, and especially since Petrescu[56] obtained a mortality of 1.2 to 2.6 per cent. in 1192 soldiers. This was ascribed to the youth and vigor of these men, but as shown by Lépine, Mosius, Finkel, Landouzy and others, this reason is not valid. All clinicians agree, however, that in order to obtain beneficial effects, large doses are necessary. Franc[57] refers to equally good results obtained with digitaline. Beates[58] and Arnold and H. C. Wood, Jr.,[59] have shown that the doses usually prescribed are practically useless.

Adrenalin and Pituitrin.—In the heart failure of advanced cases and in senile pneumonia, these agents have been found of value, especially where other stimulants failed. The action of *adrenalin* is enhanced by adding *pituitrin* in equal quantity, 8 minims (0.75 gm.) of each. Digitalis stimulates the adrenals and the production of their secretion, but in senile pneumonia, it is contraindicated because of the inability of the organs to respond to the stimulation. *Adrenalin* injected with one syringeful of saline solution very slowly is very effective in these cases. It may be given in doses not exceeding 8 minims (0.5 gm.) of a 1:1000 solution, at short intervals according to the needs of the case. *Adrenal gland,* 3 grains (0.2 gm.), every two or three hours, has been found valuable as a general stimulant.

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* *Author's conclusion.*

[53] Naegeli-Akerblom: Central. f. inn. Med., Bd. xvi, S. 769, 1895.

[54] Borini: Central. f. Bakt. u. Par., Bd. xxxii, S. 207, 1902.

[55] Von Jaksch: Central. f. klin. Med., Feb. 6, 1892.

[56] Petrescu: Le bull. médical, vol. viii, p. 237, 1894.

[57] Franc: *Ibid.*, vol. ix, p. 885, 1895.

[58] Beates: Jour. Amer. Med. Assoc., June 26, 1897.

[59] Arnold and H. C. Wood, Jr.: Amer. Jour. Med. Sci., Aug., 1900.

E. A. Gray[160] used suprarenal extract in the above doses in six cases. The stimulation was marked; the heart reacted promptly and the general-symptoms were favorably influenced, especially in aged subjects. H. L. Elsner[161] used adrenalin with advantage in several cases. In one of these its use, after strychnine had failed, promptly increased the cardiac power and the blood-pressure. S. Solis-Cohen[162] prefers suprarenalin triturate given every ten minutes with a little sugar of milk.

Other drugs have proven useful in this connection, namely, *strychnine, pilocarpine, alcohol, strophanthus, atropine, caffeine, ammonium carbonate*, and *nitroglycerin* given in the usual therapeutic doses, but *adrenalin*, injected, is more effective.

AGENTS WHICH COUNTERACT EXCESSIVE ARTERIAL TENSION AND PULMONARY ENGORGEMENT.—When the disease occurs in strong plethoric individuals, the protective reaction is so violent sometimes that the lungs become excessively congested through undue arterial tension and the heart becomes overburdened. Marked dyspnœa and even cyanosis may then occur—conditions which some clinicians meet by bleeding. This measure reduces the congestion, but, of course, at the expense of the blood's protective constituents. Viewed in this light, bleeding is an unscientific measure and is not recommended, especially since we have remedies capable of relieving the patient without compromising his prospects of recovery.

Veratrum viride, by depressing the activity of the vasomotor center, correspondingly diminishes the pulmonary engorgement since its main cause, excessive blood-pressure, is diminished through the resulting dilation of the great central trunks. The dangerous resistance to which the heart is subjected is also removed because the "patient is bled into his own circulation," as Wood says. The temperature is likewise lowered and perspiration is provoked. The tincture of veratrum viride may be used, 8 to 16 minims (0.5 to 1.0 gm.) (1905 U. S. P.) being given every two hours until the desired effect is produced. It is only indicated, however, in sthenic cases. In such, veratrum viride assists the curative process since it causes relaxation of the arterioles, thus admitting more blood—which is always rich in auto-antitoxin in sthenic cases—into the diseased area.*

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* *Author's conclusion.*

[160] E. A. Gray: Medical Record, Apr. 5, 1902.

[161] H. L. Elsner: N. Y. Med. Jour., Jan. 2, 1904.

[162] S. Solis-Cohen: Jour. Amer. Med. Assoc., Dec. 10, 1904.

H. C. Wood[103] states that although veratrum viride can produce alarming symptoms, it is the safest of cardiac depressants. Dickerson,[104] Rittenhouse,[105] Atkinson,[106] Hill,[107] Stephens,[108] and others praise it highly, the last named after using it in 54 cases. Illoway[109] also found it valuable in children in doses varying from ½ to ¼ drop (2 to 4 drops, 1905 U. S. P.) given every hour and a half.

I have obtained effects similar to those of veratrum viride by means of full doses of *sodium bromide, i.e.,* 20 to 30 grains (1.3 to 2 gm.) every three hours, giving it only until the dyspnœa was relieved. The cough and pain are also favorably influenced. Its action is similar to that of veratrum viride: by causing general vasodilation it depletes the congested areas.* It is especially useful when there is delirium.

When an immediate effect is required, *i.e.,* when there is great dyspnœa or cyanosis, *nitrite of amyl* inhalations, which cause general vasodilation, are indicated, the effect being sustained with *nitroglycerin* given internally.

The indiscriminate use of the latter drug, especially in sthenic cases, is a dangerous practice. As Hare states, "it has come to be employed with the idea that it is a circulatory stimulant, which is an entirely erroneous conception."

The management of a case of pneumonia, in the light of my views, reduces itself as regards remedies to the following general principles: (1) *creosote carbonate* in any kind of case, sthenic or asthenic, or *sodium salicylate* if creosote carbonate is not available; (2) *quinine* in asthenic cases, including alcoholics, the ill-fed, overworked and obese subjects; (3) *digitalis* or *thyroid gland,* or in emergencies *adrenalin,* when the protective reaction of the adrenal system is deficient; (4) *veratrum viride* or *the bromides* when the vascular tension is excessive in sthenic subjects as shown by dyspnœa, duskiness or cyanosis; (5) *amyl nitrite* and *nitroglycerin* when these symptoms become threatening; (6) *saline beverages* in all cases attended by fever.*

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* *Author's conclusion.*

[103] H. C. Wood: "Therapeutics," eleventh edition, 1900.
[104] Dickerson: Jour. Amer. Med. Assoc., Nov. 9, 1901.
[105] Rittenhouse: Clinical Review, Feb., 1905.
[106] Atkinson: St. Louis Med. Rev., May 18, 1901.
[107] Hill: N. C. Med. Jour., June 5, 1896.
[108] Stephens: Therap. Gaz., Nov. 15, 1901.
[109] Illoway: Pediatrics, Dec. 15, 1900.

BRONCHO-PNEUMONIA.

Synonyms.—*Capillary Bronchitis; Catarrhal Pneumonia; Lobular Pneumonia; Aspiration Pneumonia; Deglutition Pneumonia; Suffocative Catarrh.*

Definition. — Broncho-pneumonia, an inflammation of the bronchioles, lobules and often of the parenchyma of a circumscribed portion of both lungs, is due to the multiplication therein of pathogenic organisms, particularly of the pneumococcus, streptococcus pyogenes and staphylococcus pyogenes, owing to a deficiency in the mucus and mucosa of the respiratory tract, of auto-antitoxin and phagocytes, which, under normal conditions, destroy these germs and their toxins. The deficiency of these protective agents may be due either to local or general adynamia: local, as after anæsthesia, tracheotomy, prolonged inhalation of granite dust, etc.; general, as after debilitating diseases, or owing to marasmus, rickets, senility, etc., the primary cause of which, in the latter case, is hypoactivity of the adrenal system.*

Symptoms.—The development of broncho-pneumonia varies to a certain extent with the cause, but as a rule the onset is not sudden, as in pneumonia, because the initial phenomena are bronchial. These consist of a stubborn cough, a moderate rise of the temperature and pulse, vomiting and sometimes convulsions. If it develops as a complication, the primary disease changes its aspect; eruptions such as those of measles or scarlatina become less defined or disappear; the cough of pertussis loses its characteristic sound, etc.

When the pneumonic inflammatory process develops, the temperature, from perhaps 100° F. (37.8° C.) that it was before, now rises—unless the original disease be a debilitating one—to 102° F. (38.9° C.) and above—as high as 104.5° F. (40.3° C.); the pulse becomes rapid: from 120 to 150; repeated slight chills occur, and the cough becomes more severe and harassing. The febrile process is extremely irregular, both it and the pulse, which is, as a rule, feeble and frequent, varying with the intensity of the pulmonary lesions and the fluctuations of the arterial tension. As a rule, however, the temperature gradually rises during two or three days, remains at the highest point one or two days or more. Then occurs a remission, followed in turn by a new exacerbation, etc. The breathing becomes rapid, and the child soon shows evidences of distressing dyspnœa, until finally the lips and face become cyanosed. This may be followed by a leaden hue or lividity with dilation of the pupils—signs of impending dissolution.

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* Author's definition.

The child may pass away at this time, but often the accumulation of carbon dioxide in the blood dulls sensibility; the irritable cough improves and though the lividity of the face continues and the respiratory rate is very high, and the pulse suggests by its rapidity, weakness and irregularity a lethal trend, a change for the better occurs and the child is soon restored to health.

The physical signs are mainly those of bronchitis; fine sibilant and mucous râles or sonorous ronchi are heard on both sides, the percussion note being but slightly modified from the normal, though a slight increase in resonance is sometimes obtained. When the base of both lungs is involved, dullness over the diseased area, with some bronchophony and fine subcrepitant râles suggests consolidation; but if these signs are fugacious, disappearing at one time to re-appear at another, they indicate temporary exacerbations of local congestion which cease as soon as convalescence begins.

In *aged subjects* the occurrence of broncho-pneumonia is very probable when dyspnœa suddenly occurs in the course of a bronchial catarrh, the respirations rising from 26 to perhaps 40. Adynamia, dryness of the tongue and a high fever, delirium, etc., then follow in rapid succession, the typical physical signs of broncho-pneumonia soon becoming evident. Cyanosis is a more serious symptom than in children in these cases, owing to the lack of recuperative vitality which senility entails. Hence the great fatality of the disease in such subjects.

In *adults* especially in sthenic subjects, the dyspnœa is apt to become severe very early, the fever soon rising to 104° F. (40° C.). The expectoration is free and often tinged with blood, and a red spot on both cheeks attests to the kinship of the condition present to lobar pneumonia, with the physical signs of an intense bilateral bronchitis, and in many instances the general phenomena of a general typhoid state.

In *infants* the disease occurs most frequently during the first six weeks of life. The infant refuses the breast and soon shows respiratory distress, some fever or perhaps hypothermia. In some instances convulsions occur among the earliest signs of the disease, and are soon followed by its typical phenomena. It is very frequently fatal, corresponding in this particular with the broncho-pneumonia of the aged. The mortality is especially great among bottle-fed children.

Hardy[129] in a study of 150 fatal cases found that the mortality was 7.7 times as great in bottle-fed as in breast-fed children. This is readily accounted for in the light of my views by the fact that the maternal milk supplies the infant with auto-antitoxin which protects it against infection. Even fresh cow's milk fails to do this, since the reactions to which the auto-antitoxin is submitted within a few minutes after it is drawn, deprive it of its bacteriolytic and antitoxic properties. The question is a complex one which I will treat elsewhere at length.

Etiology and Pathogenesis.—Broncho-pneumonia, as its name implies, is a combination of bronchitis and pneumonia, and occurs mainly in children before the third year and in aged subjects. It is occasionally observed in the adult. In children it may develop idiopathically, *i.e.*, from a cold, beginning often with coryza or laryngitis, or both, especially when the subjects are debilitated, anæmic, poorly fed, etc. In about two-thirds of the cases, however, it occurs as a complication of measles, scarlet fever, pertussis, diphtheria, erysipelas, infantile diarrhœa and variola, often owing to exposure to draughts, inadequate covering, etc., during convalescence, while the child is still weak. We thus have precisely, as in pneumonia, a debilitated body as soil for the development of the pathogenic organisms.

The primary form is due to the pneumococcus, while the secondary form is ascribed to the streptococcus mainly, but also to other bacteria: the pneumococcus of Friedländer, the bacillus of influenza, of typhoid fever, of tuberculosis, the bacillus coli communis, etc. Most of these are derived from the upper respiratory tract and the mouth. Broncho-pneumonia may also be caused by the inhalation of stone, steel, coal and other dusts, and by the aspiration of particles of food or, in the newborn, of lochial discharges.

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[129] Hardy: Lancet, Sept. 24, 1904.

Samuel West[111] states that broncho-pneumonia is associated with several varieties of pathogenic organisms, the streptococcus, the staphylococcus, the tubercle bacillus and others, but that chief among all is the pneumococcus, which is present either alone or in association with others in at least 50 per cent. of the cases. The bucco-pharyngeal origin of the pathogenic organisms was shown by Pasteur, Netter, Thost and Besser.[112] Darier[113] states that the development of the disease is favored by diminution of the body's resistance to infection, and that all debilitating influences predispose to it. Tyson[114] also holds that "all influences depressing to life, such as overwork, fatigue, the air of badly ventilated and crowded houses, insufficient food, and defects of hygiene" act as predisposing causes.

The debilitated condition of the organism at large being attended by a corresponding condition of the adrenal system, the pulmonary secretions are inadequately supplied with auto-antitoxin and phagocytes, and the bacteria inhaled are free to multiply.* The bronchial fluids soon become, therefore, laden with pathogenic bacteria and what toxins some of them may secrete. They excite, therefore, a primary bronchitis, a local inflammatory process, which extends from the bronchi to the bronchioles, causing bronchiolitis, the so-called "capillary bronchitis." The bronchioles become obstructed through the inflammatory thickening of their walls and by the inspissated mucus secreted, and the alveoli no longer receive air. Hence the cyanosis, which corresponds in intensity with the number of alveoli rendered useless by the morbid process.

Simultaneously another pathological condition is developed, *i.e.*, involvement of the parenchyma of the lung surrounding each inflamed bronchiole. As the corresponding alveolus becomes depleted of its air, it collapses (atelectasis) and is itself soon involved in the inflammatory process. As many inflamed bronchioles and alveoli are merged together by a similar process, an area of consolidation is finally formed. This does not mean, however, that the inflamed structures are destroyed, for after death they are usually found to have retained their anatomical conformation, and may be inflated by means of a tube inserted into a bronchus. But every evidence of a very acute inflammation is present, capable, if not arrested, of finally causing obliteration of such large areas of air-cells that life becomes impossible.

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* *Author's conclusion.*

[111] Samuel West: Brit. Med. Jour., May 28, 1896.

[112] Pasteur, Netter, Thost and Besser: Cited by Darier: Debove and Achard's "Manuel de méd.," T. i, 1896.

[113] Darier: *Ibid.*

[114] Tyson: "Pract. of Medicine," third edition, p. 229, 1903.

Important in this connection is the fact that the pulmonary lesions are partly auto-protective, in the sense that the inflammatory process has for its purpose the destruction of the pathogenic organisms and their products, and the repair of destroyed tissues.* An intense hyperæmia is present, the blood-vessels being distended and tortuous, and the capillaries are so engorged that some are ruptured, allowing blood to ooze into the bronchi and stain the muco-purulent substances expectorated.

It is this intense hyperæmia that is relieved when the carbon dioxide accumulates to such a degree in the blood, that the little patient is brought to the verge of death.* If the consolidated areas are so numerous that the oxygenation becomes inadequate, dissolution follows, but if a sufficient proportion of the inflamed areas are still in a condition of atelectasis, the more or less rapid disgorgement of the capillaries of the bronchioles opens up a corresponding number of alveoli.* The additional supply of oxygen the body now receives serves to tide it over the dangerous period, until another auto-protective factor asserts itself and brings on recovery, viz., the accumulation in the blood of toxic wastes.* Indeed, gradually as the intake of oxygen is being reduced, catabolism becomes steadily more imperfect until such time when the tissues, owing to their superior affinity for it, utilize all the gas available. Filled with toxic wastes, the blood violently stimulates the previously torpid test-organ, and a flood of auto-antitoxin and a host of phagocytes invade all the fluids of the body, including the blood of the diseased area, destroying the pathogenic germs and their toxins, and the patient suddenly, as we have seen, becomes convalescent.*

Treatment.—All the cardinal measures that have stood the test of time in the treatment of this disease have a common physiological action: that of stimulating the adrenal center.* *Calomel,* one of the most active agents of this kind* at our disposal, is regarded by many practitioners as the most efficient initial remedy when given early and in sufficiently large doses to produce catharsis after a few doses have been taken, *i.e.,* $^1/_8$ to $^1/_6$ grain (0.008 to 0.01 gm.) every two hours with sodium bicarbonate, for a child under one year of age. It enhances not only the production of auto-antitoxin, but also the vulnerability of the bacteria to the phagocytes by increasing the production of thyroidase, *i.e.*, opsonin.*

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* *Author's conclusion.*

Suggestive in this connection is the fact that diphtheria *antitoxin* has been used with success, from 1000 to 3000 units being injected. It should be renewed if necessary.

Edelheit of Vienna[115] used calomel with success in broncho-pneumonia, and held that its chief property was to promote metabolic processes. Marfan gives small doses every hour.

Antitoxin was first tried by Montgomery Paton, of Australia, who considered it as a specific. It was also used by Joseph O'Malley, of Philadelphia,[116] who was also led to conclude that it is a most valuable agent, especially in secondary broncho-pneumonias, from 1000 to 3000 units being used in the cases reported. Uninterrupted convalescence followed.

Potassium or *sodium iodide,* which also stimulates the test-organ—and through it the adreno-thyroid center*—is also an efficient remedy. It may be given to children in 1- or 3-grain (0.065 or 0.2 gm.) doses every 3 hours, with a tablespoonful or more of water. *Iodoform* in ½-grain (0.03 gm.) doses, has also given excellent results. Its action is similar to that of the iodides.

Albert Abrams,[117] as a result of observations in 61 cases, reached the conclusion that the most important features of the treatment of broncho-pneumonia were compressed air and potassium iodide. Iodoform, according to Gambardella,[118] causes rapid dissipation of the pulmonary symptoms and fevers. Its unpleasant odor renders it obnoxious, however, and it offers no advantage over the iodides.

Another remedial measure which has been highly recommended is the *cold bath.* This agent, like other forms of cold, causes an accumulation of waste-products in the vessels of the skin, by lowering the catalytic activity of the cellular trypsin. It brings on, therefore, the critical period which ensues when the little patient approaches dissolution, which ends when the waste-products violently stimulate the test-organ.* It is especially indicated when the temperature is high, and contraindicated only in asthenic cases and when the cardiac action is defective. *Cold pack* to the chest is likewise beneficial and acts like the cold bath, but with less intensity.*

Le Gendre[119] holds that the temperature of the first bath should be 82° F. (27.8° C.) and last from 5 to 10 minutes; and that the following baths may be from 75° to 65° F. (23.9° to 18.4° C.), but never lower. D'Espine and Picot contend that the first bath should be at 90° to 95° F. (32.2° to 35° C.), and subsequent ones 86° F. (30° C.). Hutinel states that the most striking effects of the cold baths are an increased excretion of urine, saliva and digestive fluids—precisely the results to be expected by an increase of metabolic activity such as that which follows stimulation of the adrenal center.

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* *Author's conclusion.*

[115] Edelheit: Semaine médical, vol. xv, p. 472, 1895.

[116] Joseph O'Malley: American Medicine, Jan. 17, 1903.

[117] Albert Abrams: Medical News, Sept. 24, 1898.

[118] Gambardella: Semaine médical, vol. xviii, p. 55, 1898.

[119] Le Gendre: *Ibid.*, vol. xvi, p. 89, 1896.

Zangger[120] reported 10 cases of broncho-pneumonia in children three months to eleven years of age, in which defervescence was realised in one to four days. The author ascribes this favorable result to his method of giving the little patients from one to seven "half baths" of four to seven minutes each, the water at a temperature of from 30° to 28° C. (86° to 82.4° F.), gradually reduced to 26° or 24° C. (78.8° or 75.2° F.). The room must be moderately warm, and the child be placed in a bath-tub with only enough water in it to cover the body, leaving the breast almost uncovered with water. The child is rubbed during the bath, and after two minutes cool water is added to bring the water down to the desired temperature. The little patient is then rubbed dry with warm towels and put back to bed. These half baths are given night and morning; a little milk is given to the child before and after the bath. The diet should be milk, diluted or not, and cold spring water should be sipped frequently. The author's experience has been that these baths twice a day raise the blood-pressure, strengthen the heart, promote expectoration and soothe the nervous irritability, etc., much better than any other measure.

The wet compress system of Prof. Lemoine, of Lille, is easily carried out, and insures almost uniform success.[121] The child is stripped to the waist, and a piece of gauze (tarlatan) folded in six or eight doubles, and so cut that it reaches from the clavicles to the umbilicus in front and to the sacrum behind, and wide enough to overlap in front, is steeped in hot water, so as to remove as much of the starch as possible, and when properly wrung out it is plunged again into cold water (the temperature of the room). The gauze is then squeezed as much as possible, and applied around the thorax and the upper portion of the abdomen; a piece of oil-silk of the same size is placed over this so as to prevent evaporation. The child is then dressed and put to bed. At the end of half an hour the application is renewed, and so on as long as the symptoms (temperature over 100° F. [37.8° C.], with vesperal exacerbation, agitation, quick-breathing, etc.) require it. There exists no contraindication to these wet compresses.

Holt[122] recommends the cold bath followed by friction for infants when the temperature reaches 105° F. (40.5° C.), and the cold pack for older children.

Measures which induce congestion of the skin and thereby deplete somewhat the pulmonary congestion are preferred by some clinicians. The *mustard-paste* poultice is probably the most efficient of these external applications. They tend also to enhance the antitoxic activity of the blood by increasing its temperature, and therefore the activity of its auto-antitoxin.* The *mustard-linseed poultice* is also regarded as efficacious.

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* *Author's conclusion.*

[120] Zangger: Correspondenzblatt f. schweizer Aerzte, Bd. xxxv, S. 7, 1905.

[121] Lemoine: Cited by Albert: Thèse de Paris, 1896.

[122] Holt: Medical News, Dec. 1, 1900.

Winters[123] states that when there is filling up of the bronchial tubes and numerous moist râles, there is nothing more valuable than the mustard paste composed of 1 part of mustard to 4 of flour applied over the chest several times a day. Sheffield[124] recommends the following poultice: "5 parts each of flaxseed-meal and camphorated oil; 1 to 2 parts of mustard and a sufficient quantity of boiling water to make a thick paste by thorough stirring. This mass is spread on thin gauze or paper (two layers) and applied snugly to the chest and back. The child is then wrapped in an oiled-silk jacket, lined with absorbent cotton, and in a blanket, which, with the hyperpyrexia of the body, maintains the heat of the poultices; so that it requires renewal but three or four times in twenty-four hours."

The obstruction of the bronchioles (which admit the air into the alveoli) being due to intense congestion of their walls, a remedy capable of reducing the quantity of blood supplied to them, by causing constriction of the local arterioles, is indicated.* *Belladonna* is especially active in this particular, and is very beneficial when given in sufficiently large doses. *Opium*, given in the form of Dover's powder, acts much in the same way,* is especially effective when the cough is severe, but it tends to cause constipation, and should be avoided if possible.

Coutts[125] in a series of 60 cases only lost 2 by giving ¼-grain (0.016 gm.) doses of the extract of belladonna (B. P.) every three or four hours. Flushing and a definite scarlet rash may appear, but after a few doses the dyspnœa ceased and the temperature fell to normal. D. A. Hodghead, of San Francisco,[126] also obtained excellent results in 25 cases. He first gives calomel, $^1/_{10}$ grain (0.0065 gm.) every hour, until a free movement is obtained, and between these doses, also every hour, 2 drops of the tincture of belladonna. As improvement begins the belladonna is reduced to 1-drop doses hourly. The mortality was 5 per cent. He states that like results were obtained in three London hospitals, whereas by the older methods the mortality was 60 to 80 per cent.

The congestion of the bronchioles may also be reduced by agents which depress the functional activity of the vasomotor center, the general relaxation causing the blood to recede from the pulmonary and other capillaries.* The most active agent of this kind is *nitroglycerin*, of which $^1/_{500}$ grain (0.00013 gm.) may be given every hour to a child one year old; and it is especially valuable when the heart is oppressed and failing. *Sweet spirit of niter* is a milder agent of this kind. *Alcohol* produces the same result, but in another way, viz., by becoming itself oxidized, thus depriving the blood of some of its oxygen and reducing it in proportion to its efficiency as an antitoxic agent.*

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* *Author's conclusion.*
[123] Winters: Medical Record, June 26, 1897.
[124] Sheffield: Graetzer and Sheffield's "Pract. Ped.," p. 259, 1905.
[125] Coutts: Brit. Med. Jour., Jan. 28, 1899.
[126] D. A. Hodghead: Pacific Med. Jour., June, 1899.

When any of these remedies are used, *oxygen* inhalations should be administered simultaneously, to enrich, as much as possible, the air inhaled while the bronchioles are patent.

Late in the disease, *cardiac failure* is mainly due to failure of the adrenals. Hence intramuscular injections of *adrenalin* 1:1000 solution 5 minims (0.3 gm.) in a syringeful of saline solution repeated every three hours if required. In adults three drops of *pituitrin* in addition prolong its effects.

Text-books recommend digitalin, strophanthus and other cardiac stimulants, but their use is indicated only in asthenic cases. The heart fails in sthenic cases because the resistance of the blood-column is too great for it, and in the rest because its walls are not receiving enough blood, owing to excessive vasomotor constriction of its coronaries. Cardiac stimulants whip up the organ to drive it more rapidly to its doom. In weaklings, however, these agents are valuable.

The high fever which attends practically all cases, causes the alkaline salts of the blood to be utilized with unusual rapidity, especially sodium chloride, which is constantly being voided with the excretions and secretions, the urine, the sweat, saliva, and tears.* The blood loses its bactericidal and antitoxin activity gradually as its alkalinity is being reduced, and acidosis is becoming more manifest. Osmosis, which should be normal to insure the freedom of all secretory functions—particularly in pulmonary disorders, of the glandular elements of the bronchi—becomes markedly impaired, and the time finally comes when practically all the fluids of the body can no longer fulfill their functions.*

The aim should be, therefore, to keep the organism supplied with alkaline salts. In children old enough to expectorate, and adults, the first evidence that these salts are beginning to fail is the viscidity of the sputa, soon followed by great difficulty in "raising" them, and a marked increase of cough. *Ammonium chloride* or *carbonate*, by increasing the alkalinity of the blood, corrects these morbid phenomena. Large doses are not necessary and tend to disturb the stomach: $^1/_4$ grain (0.016 gm.) in a child under 1 year of age; $^1/_2$ grain (0.03 gm.)

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* *Author's conclusion.*

for one from 2 to 3 years old, and from 1 to 3 grains (0.065 to 0.2 gm.) for older subjects, every two hours, suffice. It should always be given with as much water as the patient will take. *Liquor ammonii acetatis* is another valuable agent, given in doses varying from 5 to 30 drops—also in considerable water—according to age.

The onset of collapse is not only advanced, but may be actually caused by the absence of sodium chloride in, or lowered alkalinity of, the blood, or both of these conditions. *Hypodermoclysis* promptly restores the patient—even when he is approaching the moribund state, in some cases. In the infant, 4 to 6 ounces (120 to 180 gms.) of normal saline solution may be injected slowly under the scapula, and renewed if necessary. Hypodermic injections of *aromatic spirits of ammonia,* 2 drachms (8 gms.), being injected into the arm, repeated as needed, have also been found useful.

Still better than all these measures is to avoid the need of them by using alkaline beverages from the start, thus keeping the blood supplied with its normal salts.* The measures indicated on page 1367 may be utilized, reducing quantities according to age. *Saline enemata, i.e.,* rectal injections of warm saline solution, are also of very great value, especially in young children.

I cannot sufficiently emphasize the importance of not waiting until the disease is far advanced, to resort to the use of alkaline beverages. Their use should begin when the patient is first seen. Quite as important is to supply the patient with fresh air, *i.e.,* air not partially deprived of any of its oxygen, and with all the water he wants to drink.

The use of normal saline solution in this disease has been found very advantageous by J. Madison Taylor[127] when used as ordinary beverage. Lemaire[128] used hypodermoclysis in 11 cases of infantile bronchopneumonia, 6 ounces (180 gm.) being injected under the skin of the abdomen or thigh in children 3 years old and over. Under that age the injections were 2 ounces (60 gm.) three times a day. All the cases recovered. Injections of the aromatic spirits of ammonia were found very effective, though somewhat painful, by H. Morell.[129] He states that the action of the remedy is noticed almost immediately, the face losing its livid color and becoming flushed.

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* *Author's conclusion.*

[127] J. Madison Taylor: Medical Record, Jan. 13, 1906.

[128] Lemaire: *Loc. cit.*

[129] H. Morell: N. Y. Med. Jour., Sept. 7, 1895.

CHAPTER XXIX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

THE ADRENAL SYSTEM IN THE CATARRHAL AND NERVOUS DISORDERS OF THE RESPIRATORY TRACT.

The four diseases studied in the present chapter are intended to exemplify the manner in which the adrenal system reacts when exogenous or endogenous irritants assail the mucosa of the respiratory tract. Under Acute Bronchitis I submit the manner in which the tracheo-bronchial mucous membrane becomes the seat of an acute inflammatory process through the operation of a factor whose pathogenic influence has been abundantly confirmed but not explained. Bronchial asthma illustrates a complication which endows the disease with its autonomy as a morbid process, namely, hypersensitiveness of the vagal center in the pituitary body—and the manner in which stricto-dilation (the mode of action of all motor-nerves) provokes muscular contraction—the minute bronchial muscles, in this instance. A kindred disorder, hay-fever, serves to indicate how the same process operates in the nasal mucosa, where the stricto-dilators regulate the flow of blood into sinuses, which thus become engorged with blood, causing the copious secretion, marked obstruction, etc., observed in this disease. This process prevails as well in acute coryza and in other disorders of the upper respiratory tract, which cannot be treated in full in this volume. The fourth disease analyzed, pertussis, exemplifies the manner in which cough is elicited by irritation: a reflex excitation of the vagal center (or trigeminal center, if the nasal field is involved), the violence of which is such in this disease as practically to exhaust the lungs of air, thus necessitating sudden and violent inspiration, the characteristic "whoop."

ACUTE BRONCHITIS.

SYNONYMS.—*Tracheobronchitis; Acute Tracheobronchitis; Acute Bronchial Catarrh.*

Definition.—Acute bronchitis, an acute catarrhal inflammation of the tracheo-bronchial mucosa, is the expression of a local protective process characterized by an increase of auto-antitoxin and phagocytes in the secretions, having for its purpose the removal or destruction of irritants carried to the mucosa either by the air (dust, vapors, etc.), or through the blood (toxic wastes, antitoxins, toxins, etc.).*

Symptoms and Pathology.—Three types of acute bronchitis may be distinguished. The first of these is the *afebrile* form, starting, as a rule, with an acute coryza, soon followed by a feeling of oppression behind the upper part of the sternum, more or less headache, languor, and sometimes muscular pains. The expectoration is at first viscid, then opaque and purulent. There is usually some hoarseness and in some cases aphonia. In normal adults this form is quite benign, but in children it may lead to broncho-pneumonia. In aged or debilitated subjects (especially if scoliotic) the congestion of the bronchial mucosa and the imperfect elimination of the pulmonary secretions may sufficiently embarrass the smaller bronchi to cause asphyxia.

The second is the *febrile* form, in which the phenomena are all much more marked, being those of a true infection, viz., severe headache and malaise, repeated chills followed by fever, which may reach 104° F. (40° C.) in the afternoon or evening. Then follow the thoracic symptoms: dyspnœa and tightness about the chest, retrosternal rawness and pain traceable upward along the trachea to the larynx. Here a sensation of pricking or tickling provokes paroxysms of severe, dry cough, attended with little or no expectoration, and very distressing on that account. Soon, however, the sputa are brought up with more ease, and finally in abundance, being at first viscid, then muco-purulent, and finally purulent. The tongue is coated and there is usually anorexia or dyspepsia. Such an attack, left to itself, usually lasts from ten days to two weeks.

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* *Author's definition.*

The third, or *secondary* form, as its name implies, occurs as a complication of other diseases, measles, typhoid fever, variola, influenza, erysipelas, scarlatina, diphtheria, etc. It differs in no way from the second or febrile form as to its symptomatology, the various phenomena enumerated being merged in with those of the primary disease.

The physical signs in all three forms vary with the intensity of the morbid process. In the afebrile form but slight. if any, change from the normal is discernible unless the case be somewhat severe and approximate the febrile form. In the latter, the dyspnœa is attended by a compensative increase of respiratory movements, and bronchial fremitus. On auscultation, the respiratory sounds are exaggerated and differ according to the caliber of the bronchi from which it originates, the larger bronchi producing a grave note resembling snoring, the smaller, a sharp whistling or sibilant note, both during respiration and expiration. As the secretion increases, the râles become moist, as when air is blown through water. These sounds are best heard posteriorly all over the chest and on both sides. In secondary acute bronchitis, the moist or subcrepitant râles begin at the base of the lungs, where dullness on percussion is noticeable, especially in certain areas.

The predominating pathological feature is hyperæmia of the capillaries of the bronchial tubes. In severe cases this may be sufficiently marked to cause tumefication and infiltratior of the bronchial mucosa, *i.e.*, a true œdema capable of materially reducing the caliber of the smaller bronchi, and even of causing asphyxia.

This is only partly due, as shown below, to a local inflammatory process caused by a vicarious elimination of pathogenic elements. The local hyperæmia coincides with the dry cough, but this is soon succeeded by increased activity of the mucous glands and the abundant secretion produced soon gives rise to a free expectoration. An abundant local leucocytosis occurring simultaneously to rid the respiratory tract of any detritus, the sputa acquire their muco-purulent character. This stage usually terminates a mild case. In the more severe cases desquamation of the ciliated epithelium takes place, followed by lesions of the deeper structures. In the bronchitis of certain infections, diphtheria, typhoid, etc., the hyperæmia may be followed by the local formation of a false membrane which, according to Cornil and Ranvier, is replete with micrococci.

Etiology and Pathogenesis.—The *exogenous* causes of acute bronchitis are those which, such as dust or irritating vapors, reach the bronchial tubes and their ramifications with the air inhaled, and are capable of irritating mechanically or chemically their mucous membrane. This form is observed mainly among individuals who are exposed to such irritation in the course of their occupation, millers, knife grinders, etc.

The majority of cases met with, however, are due to *endogenous* causes, *i.e.*, the vicarious elimination by way of the lungs, of poisons formed in the body as a result of some morbid process.* Thus, exposure to cold and damp is a most prolific source of bronchitis. The warm—and perhaps perspiring—skin is exposed to conditions, a draught for instance, which suddenly reduce its temperature. Tissue catabolism requiring a certain temperature (without which the trypsin, the ferment upon which the process depends, will fail to act), it is materially impeded as long as the exposure lasts, and quantities of toxic products of imperfect metabolism are formed.* Being gradually transferred by the lymphatic circulation to the blood-stream, these toxic wastes soon reach all parts of the body and are gradually eliminated by the urine, sweat and mucous membranes. The mucosa of the upper respiratory tract taking part in this process and being readily irritated by the special poisons (as it is by iodine and other substances), it becomes inflamed, its most sensitive portion, that lining the nasal cavities, being affected first.* The bronchitis so frequently observed among gouty subjects, and the secondary bronchitis that complicates so many infectious diseases, and also malaria, Bright's disease, etc., are all due to the same cause, *i.e.*, auto-protective elimination of the poisons through the bronchial mucosa and the local irritation engendered thereby.*

The local phenomena incident to the auto-protective process are not those, however, that give rise to the untoward or dangerous features of the disease.* These are due to swelling and œdema of the mucosa, the causes of which vary according as to whether the bronchitis be of exogenous or endogenous origin.* In the former case, these phenomena are produced directly by the irritant. In endogenous bronchitis, they are partly due to this process, the irritants being the poisons derived from the blood, that are being vicariously eliminated through the bronchial mucous membrane. The principal cause of the local lesions, however, is a constriction of all the vessels of the body, which occurs as an incidental feature of the primary causative toxæmia—toxic wastes, disease toxins, etc. The blood-mass being thus forced into the capillary system, the capillaries of the bronchi are themselves engorged—sufficiently so in severe cases to provoke marked swelling of the bronchial mucosa.

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* *Author's conclusion.*

The *exogenous form*—rarely met with—is well illustrated by six cases reported by J. N. Hall,[1] in which the causes were the inhalation respectively of chlorine gas, sulphurous-acid gas, formaldehyde, kerosene smoke and smoke containing undetermined irritants, and one by Thomas,[2] due to the inhalation of lime dust. To the same class would belong the "bacillary bronchitis" ascribed to the streptococcus by Forchheimer,[3] Patton[4] and others, and to the diplococcus pneumoniæ by Ritchie,[5] P. W. Williams[6] and other observers. Pharyngeal erysipelas and diphtheria may thus prove a source of acute bronchitis by extending downward. That under such conditions infiltration amounting to obstructive œdema may occur, is shown by the familiar lesions produced in the upper respiratory tract, the larynx, for instance, under similar circumstances. In infants it is especially apt to occur owing to the laxity of the cellular tissue.

The well-known fact that cases of gout and Bright's disease are liable to acute bronchitis and that it may appear in such subjects without exposure to cold, points to the *endogenous* cause of the disease in healthy subjects after such exposure, since both gout and Bright's disease are attended by an accumulation of toxic products of imperfect catabolism. Many bacterial infections act the same way; thus the secondary bronchitis of variola is accompanied by the specific pustular inflammation of the bronchial mucosa—a counterpart of the cutaneous inflammatory lesions due to elimination of the specific toxic elements of the disease. In some exanthems, scarlatina and measles for instance, the conjunctival, nasal, pharyngeal and bronchial mucosæ may even precede the cutaneous eruption. Lancereaux[7] contends, in fact, that "few morbid agents leave the respiratory tract absolutely intact." As is well known, iodine, when given but slightly in excess of the quantity utilized by the body, causes "iodism," including cough in some cases, through a process similar in every respect to that which prevails in any form of endogenous bronchitis. In all these causative conditions the general blood-pressure is raised. In the febrile infections it is high owing to the fever itself, as shown by the flushed face, the excessive warmth of the skin, etc.; gout, Bright's disease and malaria, for example, are also attended, as is well known, by periodical elevations of the blood-pressure.

Treatment.—The two main indications in view of the pathogenesis of the disease are: (1) to counteract the *general* vasoconstriction and relieve the engorgement of the bronchial capillaries;* (2) to promote elimination through normal channels, *the kidneys, intestines and skin, of the toxic substances, which*, by being vicariously eliminated by way of the lungs, provoke the bronchial hyperæmia.

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[1] J. N. Hall: Phila. Med. Jour., Dec. 20, 1902.
[2] Thomas: Atlanta Med. & Surg. Jour., Dec., 1888.
[3] Forchheimer: Med. News, June 1, 1901.
[4] Patton: N. Y. Med. Jour., Mar. 22, 1902.
[5] Ritchie: Jour. Path. and Bact., vol. vii, p. 1, 1901.
[6] P. W. Williams: Bristol Med.-Chir. Jour., June, 1902.
[7] Lancereaux: Gaz. des hôpitaux, vol. lxviii, p. 1061, 1895.

Both these indications are materially facilitated if the patient can be kept in bed. The formation of wastes which attends physical exertion is thereby limited to its lowest degree, and what catabolic and oxidizing energy the blood can spare over and above that required for tissue metabolism, is entirely utilized for the destruction of the pathogenic elements. Even the vascular tension is favorably influenced, since the waste-products developed during muscular activity tend to raise the blood-pressure. The warmth of the bed also exercises a favorable influence by causing blood to circulate more freely in the skin, and by facilitating diaphoresis.

In the average case, remedies which lower directly the blood-pressure may be advantageously employed, especially in view of the fact that they tend to relieve simultaneously the harassing dry cough, and to reduce greatly the character of œdematous infiltration of the bronchial mucosa. The *sodium bromide*, 15 grains (1 gm.) and *chloral hydrate*, 10 grains (0.6 gm.), given jointly every three hours in a solution containing merely simple syrup or syrup of lemons (but no expectorant) soon procure these results and afford the patient considerable relief, by depressing the sensitiveness of the general vasomotor center.*

Some of my own cases were relieved after a couple of doses of this mixture, though the dyspnœa was already troublesome. Its use must be avoided in debilitated subjects, however, since their auto-protective functions would be further weakened. Persons otherwise in normal health are not materially influenced in this direction, and the pathogenic poisons in the body-fluids are gradually catabolized and eliminated by the normal paths.

When these agents cannot be employed, *veratrum viride*, 10 minims of the tincture (0.6 gm., 1905 U. S. P.) every hour, three times, then every two hours, may be given instead. Although its physiological effect is almost similar, it tends to cause general depression in some cases, and does not always moderate the cough. When there is oppression, an indication that oxygenation is being hampered in the smaller bronchi, it replaces advantageously the chloral hydrate. *Aconite*, in drop doses (1905 U. S. P.) every hour, is preferred by some authors.

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* *Author's conclusion.*

Stimulation, the use of balsams and expectorants, do more harm at this stage than good. A reliable preparation of veratrum viride, for instance, should be prescribed, as the tinctures obtained in the shops cannot always be depended upon.

When, as is usually the case, the patient cannot be prevailed upon to remain at home, the same results may be obtained by remedies which counteract the bronchial hyperæmia, by causing, through their stimulating action on the sympathetic center, constriction of all arterioles.* In this manner, the blood cannot reach the capillaries freely, and their engorgement is prevented.* Opiates are the most reliable agents of this kind. *Dover's powder*, 10 grains (0.6 gm.) taken at bedtime with a large tumberful of water, is especially advantageous, since its ipecacuanha counteracts the evil effects of the opium by promoting diaphoresis and hepatic activity—the main antitoxic resource of the organism. During the succeeding day, Dover's powder should not be used, however, since the diaphoresis produced exposes the patient to the effects of cold. The beneficial action on the lungs may be sustained, however, with *heroin*, $^1/_8$ grain (0.008 gm.) every three hours, and the Dover's powder resumed the second night, the dose being reduced, however, to 5 grains (0.3 gm.). *Codeine*, in doses of $^1/_4$ to $^1/_2$ grain (0.016 to 0.03 gm.), is preferred by some physicians. If constipation occurs (in adults) a full dose of *citrate of magnesia* is indicated to enhance the elimination of the pathogenic toxics by the intestinal canal.

In the acute bronchitis of infancy and childhood, opiates do not act as satisfactorily. *Calomel*, $^1/_6$ grain (0.01 gm.), rubbed up with sugar and milk and given every two or three hours, produces, after a few doses have been taken, a copious evacuation of the bowels and disappearance of the morbid symptoms, including fever, if the case belong to the febrile form Active stimulation of the adrenal center and a rapid increase of the auto-antitoxin, is obviously the effect produced under these conditions.*

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* *Author's conclusion.*

In some cases, the dyspnœa is sufficiently marked to demand more active measures to lower the blood-pressure.* A few whiffs of *iodide of ethyl,* inhaled from a handkerchief upon which 10 drops of this remedy have been poured, relieve the distressing symptom in a few minutes. *Nitrite of sodium,* 1 grain (0.065 gm.), in a little water, produces a similar but more lasting effect. Inhalations of *oxygen* are of great value when a tendency to cyanosis occurs.

The importance of this symptom was emphasized by B. W. Richardson,[8] Bruce[9] and others. It comes on late in the course of the disease, and is complicated by the accumulation of fluids in the smaller bronchi. Many cases of acute bronchitis in which "shortness of breath" is complained of, are nearer asphyxia than they are thought to be by their physicians. Nitrite of sodium and nitroglycerin have been recommended by Fraser,[10] and iodide of ethyl by Main[11] and others. Oxygen is spoken of as a life-saving measure by Sinainski,[12] Langston,[13] Leech[14] and many other observers.

An important feature of the treatment of febrile bronchitis is the ingestion of alkaline fluids to facilitate the elimination of toxic wastes by the kidneys, and antagonize acidosis, as indicated on page 1367. When the acute stage recedes, the elimination of the bronchial detritus must also be facilitated by remedies which increase the alkalinity of the blood and facilitate general osmosis, including that of the peribronchial fluids.* *Ammonium chloride* is an active remedy of this kind, in 10-grain (0.6 gm.) doses every three hours, given in a mixture containing 30 minims (1.85 c.c.) of syrup of tolu to the dose.

If the convalescence is delayed, the chloride may be replaced by *ammonium iodide,* which stimulates somewhat the adrenal system, owing to the iodine it contains. More active in this connection, however, is a mixture containing *potassium iodide* and *ammonium carbonate,* 5 grains (0.3 gm.) of the former and 10 grains (0.6 gm.) of the latter to the dose. This combination is very effective in children, the dose, of course, being adjusted to the age of the little patient.

When after recovery from the more acute symptoms, cough and a muco-purulent expectoration persist, the fluid extract of *hydrastis*, 20 to 30 drops, four times daily, in a little sweetened water, is sometimes quite efficacious, acting much like the opiates without being attended by their untoward effects. *Caffeine*, 5 to 10 grains (0.3 to 0.6 gm.), in a solution containing 20 grains (1.3 gm.) of *potassium acetate*, administered on retiring, is to be preferred when the cough is troublesome at night. *Apomorphine*, in doses varying from $^1/_{20}$ to $^1/_2$ grain (0.002 to 0.03 gm.), given after meals to prevent nausea, is preferred by some authors.

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* *Author's conclusion.*

[8] B. W. Richardson: Med. Press and Cir., Jan. 25, 1893.

[9] Bruce: Lancet, May 30, 1891.

[10] Fraser: Amer. Jour. Med. Sci., Feb., 1893.

[11] Main: Brit. Med. Jour., Nov. 30, 1889.

[12] Sinainski: Lancet, Sept. 1, 1888.

[13] Langston: Brit. Med. Jour., Jan. 30, 1892.

[14] Leech: Practitioner, May, 1894.

In some cases, all these measures prove ineffectual, owing to general asthenia. *Quinine hydrochlorate*, 2 grains (0.13 gm.), given with *strychnine*, $^1/_{40}$ grain (0.0016 gm.), after each meal, is often effective in such cases, owing to its stimulating action on the general centers. A more lasting effect is obtained by means of small doses, *i.e.*, 1 grain (0.065 gm.) of *thyroid extract*, three times daily, after meals.* By enhancing physiologically the functional activity of the adrenal system it activates that of all functions and augments general nutrition.*

BRONCHIAL ASTHMA.

SYNONYMS.—*Asthma; Spasmodic Asthma.*

Definition.—A form of paroxysmal dyspnœa due to the concurrence of two pathogenic factors: (1) hyperexcitability of the general vagal center; (2) the presence within or upon the bronchial mucosa, of endogenous or exogenous irritants. The mucosa requiring for the expulsion of these irritants, reflex impulses derived from the general vagal center, the hyperexcitability of the latter causes it to project unusually violent impulses to all the elements of the bronchi, including their muscles, and these in turn, being inordinately contracted, they reduce the caliber of the bronchi and thus provoke asthma.**

Symptoms.—An attack of asthma may be preceded by one or more premonitory symptoms: slight gastro-intestinal malaise, flatulency, intellectual torpor or exuberance, depression of spirits, pruritus, especially of the trunk and chin, sneezing, accompanied sometimes by a free flow of watery mucus, epistaxis, and in most cases a copious excretion of urine.

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* *Author's conclusion.*

** *Author's definition.*

The access proper usually begins abruptly, often during the early morning hours. Marked restlessness is soon followed by dyspnœa of the most distressing kind, and a sensation of great depression about the chest. The patient soon finds it necessary to assume positions that favor the action of the respiratory muscles, which seem unable to cause depression of the thorax and expulsion of the air. Gradually, as this difficulty increases, the dyspnœa becomes more distressing until, after a couple of hours or more, the face becomes dusky and perhaps cyanotic, owing to imperfect oxygenation. In severe cases, this phenomenon is sufficiently marked to cause marked hypothermia, especially of the extremities. The signs of asphyxia are so intense in some cases, that they may suggest, even to the physician, an early lethal termination. The pulse is small and rapid, the brow is bedewed with sweat, the eyes stand out prominently, a deadly pallor replaces the cyanotic hue, etc.

The movements of the chest are suggestive. Though fully expanded, it fails to recede to any marked extent during expiration. The inspirations are short, but the expirations are considerably prolonged, thus reversing the normal relations between the respiratory acts. The percussion note is hyperresonant, sometimes almost tympanic, but highly-pitched. Auscultation confirms the objective respiratory phenomena: the expiration is greatly prolonged, and both inspiration and expiration are attended by sibilant, more or less high-pitched râles, throughout the entire chest, which resemble the chirping of a multitude of birds. The heart is often displaced, the apex being nearer the sternum and lower down than usual—obviously pushed in this unusual position by the distended left lung. The veins of the neck are, as a rule, considerably dilated.

When the paroxysm has reached its worst stage, the picture changes: the breathing becomes easier, and a spell of tight, harassing cough marks the onset of the period of resolution. At first the sputa are quite characteristic of asthma. They contain small, grayish-white gelatinous pellets, Laennec's "pearls," which are in reality small rolls of condensed mucus, containing two characteristic elements, Curschmann's spirals and the Charcot-Leyden crystals. The spirals are skeins of spirally-disposed mucin filaments enclosing many eosinophile leucocytes;

the crystals are similar to those found in the blood in leukæmia. An enormous number of free eosinophile leucocytes are also found in the sputum, as well as in the blood. Gradually, however, the expectoration assumes the ordinary mucoid type; as it becomes freer the cough becomes less harassing, and the attack passes off, leaving the patient considerably weakened.

The relief may be of short duration, a second attack following the first after a few hours. As a rule, however, the paroxysm does not occur until the succeeding night, more or less coughing and wheezing occurring in the interval. Paroxysms may thus reappear five or six nights in succession, the series constituting an "attack" of asthma. The patients may then remain free several weeks, or even months, and suddenly lapse into another period of suffering.

In true bronchial asthma, the intensity of the symptoms is independent of the duration of the disease. Thus, the attacks that occur soon after its first appearance may be very intense as to dyspnœa, while in individuals who have long suffered from the disease, this symptom may not be severe. In the former cases, however, the attack passes off entirely, leaving the patient perfectly normal during the intervals, while in the latter, the bronchial mucosa may become the seat of a chronic inflammatory process, *i.e., a true* chronic bronchitis, with all its possible complications.

Pathogenesis and Pathology.—An attack of bronchial asthma is due to vagal stricto-dilation of the bronchial arterioles.* An excess of blood being admitted into the bronchial muscle-elements, and into the mucosa, the caliber of the bronchi is reduced in two ways: (1) by contraction of their muscles, and (2) by congestive swelling of the bronchial mucous membrane. In severe attacks the lumina of the terminal bronchioles becomes sufficiently reduced to prevent the egress of air from the alveoli, hence the cyanosis and the inability of the thorax and the diaphragm to contract.

All the theories best sustained by experimental and clinical evidence implicate the nervous system in the morbid process. Whether with Lefèvre, Salter, Biernier, Trousseau and others we ascribe asthma to spasm of the bronchial muscles; with Hack, Daly and others to reflex irritation of the nasal cavities; with Parrot to reflex excitation of the

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* *Author's conclusion.*

bronchial secretory elements; with Brissaud to hysteria; or with Weber to vasomotor turgescence of the bronchial mucosa, etc., the nervous system stands out prominently as an active factor at least of the salient phenomena of the disease, the bronchial obstruction. The unanimity ceases, however, when the identity of the system of nerves involved is sought. Are we dealing with a vagal neurosis, as taught by Trousseau and his school, or with a vasomotor neurosis, as taught by Weber and his followers?

The question of course is closely associated with the character of bronchial lesions. Here, again, the bulk of evidence points in the one direction, *i.e.*, Traube's view that the bronchial mucosa is the seat of a fluctionary hyperæmia which Sir Andrew Clark, Störch and others interpret as a diffuse "vaso-turgescence" or hyperæmic swelling. Not only was Fraenkel[15] able to verify this fact post-mortem, but he found the lesions peculiar to an advanced stage of local congestion, *i.e.*, of chronic bronchitis, widespread desquamation of epithelial cells. In a very interesting case recorded by J. S. Billings, Jr.,[16] such a vaso-neurotic swelling involved "the forearms and arms as high as the middle of the biceps muscles." Although the fingers were not swollen, they had been "cold and blue from the first." The "typical asthma, with nocturnal attacks of sudden onset, ending in violent paroxysms of coughing with scanty viscid expectoration," ceased, and the swelling of the arms and forearms disappeared under what, as we will see, I regard as the appropriate treatment for asthma. The pulmonary lesions and those of the extremities were evidently similar, *i.e.*, a fluctionary hyperæmia of nervous origin. That this vascular turgescence is general is suggested by the observation of Sihle[17] that in all asthmatics, both during the attacks and in the intervals, the inferior border of the liver is considerably lowered and sensitive to pressure.

The identity of the system of nerves involved at once suggests itself, *i.e.*, the vasomotor system, in accord with the views of Weber and many other observers. When, however, the manner in which such widespread results must be produced by this system is analyzed in the face of experimental evidence, it fails to meet the needs of the morbid process. In order thus to influence the general vascular system, the original cause of the disease, whether it be "uric acid" or any other systemic poison, should stimulate the vasomotor center, and produce general vaso-constriction; more blood being projected into the capillary system, the bronchial capillaries among others would become engorged, i.e., hyperæmic. That such a general vaso-constriction does not occur, however, is shown by the fact that the blood-pressure, which is raised when the systemic vessels contract, is on the contrary lowered, as shown by Sihle, the average being from 70 to 100 in a large number of asthmatics as compared to the average of 80 to 130 in normal individuals. Again, if the data upon which the vasomotor theory is based are carefully scrutinized, they are found wanting. Stimulation of the pulmonary vasomotors produces the reverse of hyperæmia, *i.e.*, ischæmia, and the many symptoms other than asthma observed that are ascribed to vasomotor influence, rhinorrhœa, ptyalism, lachrymation, diarrhœa, etc., are in reality due to overstimulation of the respective organs by their secreto-motor nerves—all of which, as I have shown in the eighteenth chapter, fulfills functions identical to those of the vagus.

Quite another picture is presented, however, when the asthma, in accord with Trousseau's interpretation, is ascribed to the vagus. Brodie and Dixon[18] recently confirmed experimentally the well-known fact that stimulation of the vagus causes a marked diminution of the volume of air entering and leaving the corresponding lung, owing to contraction of the bronchial muscles. Kingscote[19] states, moreover, that this procedure causes simultaneously spasmodic contraction of the diaphragmatic muscle. As stated by Loque,[20] moreover, a similar effect is produced when the pulmonary ends of the nerve, *i.e.*, the bronchial muscles *per se*, are excited.

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[15] Fraenkel: Zeit. f. klin. Med., Bd. xxxv, S. 559, 1898.
[16] J. S. Billings, Jr.: N. Y. Med. Jour., May 22, 1897.
[17] Sihle: Wiener klin. Woch., Bd. xvi, S. 85, 1903.
[18] Brodie and Dixon: Trans. Pathol. Soc. of London, vol. liv, p. 17, 1903.

The manner in which these phenomena are produced is made evident when the observations of Sihle,[21] that this procedure produces bronchostenosis, "the efferent path being certainly the vagi;" and that of W. Blair Bell,[22] that pulmonary terminations produce *active* vasodilation of the bronchial arteries, are interpreted from my standpoint, *i.e.*, with the vagus as a *stricto-dilator* nerve in common with all motor nerves. Indeed, stricto-dilation means, as I have shown, constriction of the vasa vasorum of the arterioles that supply muscles (as well as any other organ); the walls of these arterioles being supplied with less blood, they dilate, admitting in turn more blood into the muscular elements. Now we have in its action upon the diaphragm, proof that the vagus causes muscular contraction. Hence, in accord with the interpretation of Lefèvre, Salter, Trousseau, C. J. B. Williams and many others, the spasmodic contraction of the bronchial muscles which, by greatly narrowing the caliber of the bronchi, provokes the asthma. Hence, also, the "hyperæmic swelling" upon which Traube, Sir Andrew Clarke and others have laid stress, since stricto-dilation of the bronchial arterioles produces congestion of all the bronchial elements.

As emphasized by H. L. Swain,[23] the researches of W. S. Miller have shown that venous trunks are practically absent in the bronchial mucosa, which is thus supplied only with capillaries. The readiness with which the mucosa can become hyperæmic, and conversely the rapidity with which the capillaries can be depleted as soon as the excess of blood supplied to them is reduced (by sympathetic constriction of the arterioles as shown below), is self-evident.

The predisposing cause of bronchial asthma is hypersensitiveness of the vagal center in the posterior pituitary body.* Under normal conditions, that is to say, when the bronchial mucous membrane is not irritated by some substance brought to it by the air current or by the blood, this hypersensitiveness gives rise to no untoward phenomena. When, however, irritating particles are inhaled and reach the lungs, or when catabolism is imperfect and toxic products of hypocatabolism are eliminated (in part) by the bronchial mucosa, asthma occurs.*

The muscular constriction of the bronchi and the swelling of the mucosa which give rise to asthma, are not caused, however, by a direct action of these poisons upon the bronchial muscles, or the epithelial or secretory elements of the mucosa,

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* *Author's conclusion.*

[19] Kingscote: Brit. Med. Jour., Oct. 13, 1900.

[20] Loque: Jour. des sci. méd. de Lille, Jan. 19, 1895.

[21] Sihle: *Loc. cit.*

[22] W. Blair Bell: Edinburgh Med. Jour., Oct., 1899.

[23] H. L. Swain: Yale Med. Jour., Aug., 1900.

*but by their irritating influence upon the bronchial sensory end-organs of the vagus.** *The afferent impulses from the bronchi thus generated and transmitted to the vagal center, would evoke, if the latter were normal, just sufficiently energetic recurrent, i.e., efferent-motor, impulses to insure the elimination of the poisonous wastes (by causing periodical contractions of the bronchi, increasing the secretion of mucus, promoting the activity of the ciliated epithelium, etc.); but being hypersensitive, the center projects excessively violent stimuli to the bronchial muscles and mucosa, and the resulting bronchostenosis, produced in the manner described, gives rise to asthma.**

Reflex asthma differs from true bronchial asthma only in that the sensory impulses which excite the hypersensitive vagal center, and through it evoke the asthma, are derived from irritated surfaces other than those of the lungs, *i.e.*, the nose, the ear, etc.*

In this process the functions of the bronchial mucous membrane are assimilated to that of the stomach,* when, as shown by Pawlow, the presence of food provokes the secretion of gastric juice and the gastric muscular movements by exciting the sensory vagal terminals. We have seen that such a conclusion is warranted. The recurrent motor impulses originate, of course, from the vagal center. Since all impulses of common sensibility reach the posterior pituitary, while all coördinated involuntary motor impulses arise from this organ,* it becomes the normal source of this class of stimuli to the lungs as well.

That it is a general center which is hypersensitive—one capable of responding to impulses received from many sources—is shown by the multiplicity of conditions by which asthma may be provoked. The asthma caused reflexly by nasal and aural polypi, excitation of sensitive spots in the nasal cavities, ethmoiditis (Emerson,[54] Coggeshall[55] and others), abscess of the antrum (Richardson[56]), uterine disorders (Katz,[57] Strübing,[58] von Leyden and others), etc., illustrates this fact. With the general vagal center as the source of the asthmogenic impulses, the manner in which such lesions can produce reflex asthma becomes plain. Though unable to describe the paths followed, Schadewaldt[59] and others consider nasal asthma a trigeminal neurosis. If the pituitary's vagal center is made the terminal of sensory impulses from the nose, and the vagal efferent nerves the transmitter of motor impulses to the lungs, the reflex arc is complete.* Moreover, the actual participation of the pituitary body in such phenomena is well shown by the experiments of Cyon, who found that destruction of this organ completely annulled the reflex sensibility of the nasal mucosa.

That asthmatics suffer from hypocatabolism is well known; this is emphasized by the prominence given uric acid and the gouty diathesis as a cause of the disease by many authors. We have seen the all-importance of toxic wastes in the causation of epileptic fits. Taylor[30] and others have reported cases in which it replaced the fits. Sciatica, migraine, angina pectoris and other conditions due to toxic wastes are frequently observed in asthmatics. Again, the so-called "renal" asthma is obviously due to retention of excrementitious products in the blood. Indeed, MacIlwaine[31] has laid stress on the importance of albuminuria as a precursory symptom of this condition. Moncorgé,[32] F. Ehrlich,[33] Lemonnyer[34] and others have illustrated the influence of a rheumatic diathesis by a number of cases. All these instances are necessarily results of a debilitated condition of the organism. Aside, however, from the cases in which such a debilitated condition occurs without apparent cause, are others in which it is directly traceable to disease or habits which undermined the patient's health. As to the former, in a study of 40 cases of hay-fever, several of which were complicated with asthma, I[35] found that almost all had suffered from several of the diseases of childhood. Kissel[36] has observed the same fact in 4 cases of bronchial asthma in children, though the disease is rare in childhood. Crookshank[37] has described, under the term "asthma sexualis," cases of asthma which followed sexual excesses in both sexes. It may also, as shown by Fiessinger,[38] occur as a complication of true neurasthenia.

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* *Author's conclusion.*

[54] Emerson: Boston Med. and Surg. Jour., May 30, 1901.

[55] Coggeshall: Medical Record, June 3, 1905.

[56] Richardson: Laryngoscope, Aug., 1899.

[57] Katz: Deut. med. Woch., Bd. xxii, S. 804, 1896.

[58] Strübing: Zeit. f. klin. Med., Bd. xxx, S. 1, 1896.

[59] Schadewaldt: Verhandl. Berl. med. Gesellschaft, Bd. xvii, S. 225, 1887.

Closely related to the products of hypocatabolism as primary causes of bronchial asthma is the so-called "dyspepsia asthma" which Albu and others have ascribed to auto-intoxication. Landi[39] found that emetics and purgatives caused prompt relief in such cases. In 5 cases reported by Murdoch[40] the asthma occurred after meals and yielded readily to treatment of the stomach. In 31 cases observed by Einhorn[41] the attacks of asthma occurred either immediately after meals or two or three hours later—a suggestive coincidence with the period of assimilation.

Aside from these endogenous excitants, however, are many others of exogenous origin which are capable, as is well known, of provoking typical attacks of bronchial asthma: dust, emanations, pollen, smoke, etc. This affords self-evident proof that, however produced, asthma is primarily due to an excitant—whether applied to the sensory terminals of the bronchial mucosa or any other mucosa. As everyone is exposed more or less to the morbid effects of such irritants, asthmatics must be particularly susceptible to these irritants: a fact readily explained by the hyperexcitability of their general vagal center.

Treatment.—REMEDIES WHICH ARREST THE PAROXYSM.—This is, of course, the first indication. The bronchostenosis being mainly caused by contraction of the bronchial muscles, and thus, in turn, being due to stricto-dilation of the arterioles through which the capillaries of these muscles receive their blood, our aim should be to provoke contraction of the arterioles. As these vessels are constricted by sympathetic fibers, agents which stimulate the sympathetic center are indicated. Prominent among these is *belladonna,* especially when its alkaloid, *atropine,* is employed hypodermically. The best results are obtained when 1/120 to 1/60 grain (0.0005 to 0.001 gm.)—according to the strength of the patient—is thus given, with morphine 1/8 to 1/4 grain (0.008 to 0.016 gm.), which also promotes contraction of the arterioles and relieves thereby the bronchial hyperæmia. Relief is also afforded by burning paper previously dipped in a strong solution of *potassium nitrate* and an infusion of *stramonium* and dried, and inhaling the smoke. Cigarettes composed of *stramonium, hyoscyamus* and *cannabis Indica,* and others, such as Espic's, available in all drug-stores, are composed of agents which act like belladonna and promptly relieve the attack when smoked. In Germany, Neumeier's cigarettes, containing *lobelia, stramonium, sodium nitrate, potassium nitrate* and *potassium iodide,* are extensively used.

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[30] Taylor: N. Y. Med. Jour., Oct. 21, 1899.
[31] MacIlwaine: Med. Press and Circular, Sept. 19, 1900.
[32] Moncorgé: Lyon médical, vol. lxxix, p. 175, 1895.
[33] F. Ehrlich: Archiv f. Verdauungskrankheiten, Bd. v, S. 126, 1899.
[34] Lemonnyer: Thèse de Paris, 1902.
[35] Sajous: "Lectures on the Diseases of the Nose and Throat," Phila., 1885.
[36] Kissel: Wratch, No. 16, 1894.
[37] Crookshank: Edinburgh Med. Jour., June, 1899.
[38] Fiessinger: Jour. de practiciens, Nov. 1, 1902.
[39] Landi: Clinica moderna, Ann. v, No. 24, 1899.
[40] Murdoch: N. Y. Med. Jour., Jan. 12, 1901.
[41] Einhorn: Jour. Amer. Med. Assoc., Feb. 1, 1902.

The coal-tar derivatives, *antipyrin, acetanilid, phenacetin,* which likewise stimulate the sympathetic center, are sometimes useful. *Paraldehyde* has been recommended in doses ranging from 45 to 60 grains (3 to 4 gms.). *Adrenalin* 8 drops of the 1:1000 solution, in 1 dram (4 gms.) of saline solution, intramuscularly acts promptly. (See also pages 14 and 761, vol. i.)

Atropine, first used by Trousseau, has more recently been revived and highly recommended by Von Noorden[42] and Riegel.[43] The former begins with 1/120 grain (0.0005 gm.) and gradually increases the dose to 1/10 grain (0.0065 gm.). I have been using it over twenty-five years, and prefer 1/120 grain (0.0005 gm.) combined with 1/4 grain (0.016 gm.) of morphine to produce an immediate effect, repeating the dose in two hours if necessary. F. P. Hearder[44] obtained rapid and complete relief in the majority of 30 cases in which he used paraldehyde in the doses mentioned. Whitaker[45] reported a case in which 45 grains (3 gms.) caused collapse which lasted two days.

MEASURES WHICH TEND TO REMOVE THE CAUSE.—The irritability of the vagal center (which may be influenced by afferent impulses from any portion of the body) may be perpetuated by any condition which causes it to receive a continuous flow of afferent impulses, differing from those normally received only in that they are more energetic.* Nasal polypi or exostoses, by pressing on the nasal terminals of the fifth nerve, may thus transmit a stream of stimuli to the pituitary body and keep its centers turgescent and hypersensitive.* Hence, all organs within reach, the nose, the ears, the uterus, etc., should be examined to ascertain whether the predisposing cause of the asthma be not located therein. The peripheral organs are merely hyperæsthetic in some cases, and the contact of irritating substance—dust, smoke, etc., in the case of the upper respiratory tract—suffices to provoke asthma. The source of the primary central irritability may also be a localized chronic congestion, *i.e.*, hypertrophic rhinitis, gastritis, bronchitis, cystitis, etc., and slight additional irritation of these structures by substances inhaled or ingested may bring on a paroxysm by further exciting the already hyperæsthetic center. The liability to attacks of asthma cannot be removed unless any such cause of central irritation be eradicated.

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* *Author's conclusion.*

[42] Von Noorden: Therap. Monats., Bd. xii, S. [illegible], 1898.

[43] Riegel: Deut. med. Woch., Bd. xxv, S. [illegible], 1899.

[44] F. P. Hearder: Brit. Med. Jour., Mar. 21, 1896.

[45] Whitaker: N. Y. Med. Jour., May 2, 1896.

In some of these cases paroxysmal sneezing, to which the patient attaches but little importance, points to the source of the central irritation. By passing a probe over the Schneiderian membrane sensitive areas are frequently found which provoke sneezing, cough and even dyspnœa when touched. Chromic or glacial acetic acid applied to these areas suffices in some instances to prevent further accesses. In such cases the local application of a 10 per cent. solution of cocaine in the midst of an attack of asthma will arrest it. Pawinski[46] observed a case in which the retention of urine was the cause of the paroxysms, these passing off as soon as the patient was catheterized. Boas[47] has reported several cases in which mild dyspeptic symptoms were followed by severe asthma and diffuse perspiration which lasted until the gastric disorder had disappeared or had been relieved by emesis. In asthmatic children whose breath is foul, the tongue furred, Landi[48] obtained immediate relief from emetics or purgatives. These few examples illustrate the fact that asthma is a neurosis which may be caused by a multitude of conditions, and that it is only by a diligent search that the physician can discern the primary cause of the disease.

When the cause of the disease cannot be traced to any localized disorder, the central hyperexcitability is the result of repeated irritation by the toxins or endotoxins of several diseases acquired in rapid succession—the diseases of childhood, for instance—or it is due to the constant irritation to which toxic products of hypocatabolism submit the central neurons.* In either case the asthmogenic agents are the same: an excess of these toxic wastes in the blood.* As their presence therein is due to imperfect metabolism, the aim should be to enhance this process. *Potassium iodide* is recognized as the most beneficial agent we possess when given in doses of from 5 to 10 grains (0.3 to 0.6 gm.), three or more times a day, according to the severity of the case. This agent produces its effects by actively stimulating the adrenal center, thus causing a marked increase of auto-antitoxin in the blood.* The products of metabolism being adequately catabolized and converted into benign eliminable products, the vagus center and the bronchial mucosa are no longer irritated and the paroxysms of asthma finally cease. *Thyroid gland*, in ½ to 1 grain (0.03 to 0.06 gm.) doses, acts in the same way, and is especially useful in children (in correspondingly smaller doses) and as a substitute for potassium iodide when this agent is not well borne.* *Adrenal gland,* in 2-grain (0.13 gm.) doses may be combined with it advantageously.

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* *Author's conclusion.*

[46] Pawinski: Revue de méd., vol. xix, p. 319, 1899.

[47] Boas: Berl. klin. Woch., Bd. xxxiii, S. 882, 1896.

[48] Landi: *Loc. cit.*

The disease is readily controlled by giving potassium iodide, 5 grains (0.3 gm.), and the tincture of belladonna, 5 minims (0.3 gm.), together in a mixture every three hours at first, then the iodine alone in 10-grain (0.6 gm.) doses in a tumblerful of water during each meal. If there remains some tendency to dyspnœa, 1 grain (0.065 gm.) of thyroid gland after each meal will serve to dissipate it. In uncomplicated cases this plan is very effectual. The iodide may be increased to 20 grains (1.3 gms.) three times daily if needed. As stated by Hare,[49] asthmatics bear large doses of this agent without causing iodism.

An interesting feature in connection with effects I ascribe to the iodides and thyroid, *i.e.*, an increase of auto-antitoxin in the blood, is the observation of Revilliod[50] that diphtheria antitoxin—which is similar to the endogenous antitoxin as regards constituents—had proved very beneficial in severe cases. Suggestive also is the beneficial though ephemeral influence of adrenal extract and adrenalin, noted by S. Solis-Cohen,[51] Bullowa and Kaplan[52] and others. As emphasized by S. Solis-Cohen, however,[53] it is powerless to relieve an acute paroxysm, but tends, when given during the intervals, to diminish the tendency to recurrence. The iodides and thyroid produce the effects of diphtheria antitoxin and adrenalin, but far more efficaciously by stimulating persistently the adrenal center.

An important feature of the treatment of asthma is the *diet*. The attacks occur at night in the majority of cases, because during sleep all vital processes are somewhat depressed. Catabolism being correspondingly less active, toxic wastes accumulate in the blood and finally provoke the attack. A light evening meal, without meat, is, therefore, indicated. In severe cases, especially when the dyspnœa is continuous, a *milk diet* of three or four weeks' duration, followed by a frugal mixed diet of milk and vegetables, in which meat is partaken of but once daily, and at the midday meal, is almost curative, the milk diet being resumed when the asthma tends to recur.

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* *Author's conclusion.*

[49] Hare: College and Clinical Record, Dec., 1894.

[50] Revilliod: Rev. med. de la Suisse Romande, vol. xvii, p. 669, 1897.

[51] S. Solis-Cohen: Jour. Amer. Med. Assoc., May 12, 1900.

[52] Bullowa and Kaplan: Medical News, Oct. 24, 1903.

[53] S. Solis-Cohen: Phila. Med. Jour., Oct. 15, 1898.

Alcohol is contraindicated, since it deoxidizes the blood; pure water, on the other hand, when drunk freely, facilitates the work of the kidneys by lowering the specific gravity of the fluids passed through them. The bowels should move freely, mild saline laxatives being used when necessary.

The plain dietetic measures embodied in the first paragraph, recommended by Huchard,[54] will be found very effective. Thorowgood[55] refers to cases in which reduction of the diet alone gave rise to remarkable relief. Many instances of this kind have been recorded.

HYPERÆSTHETIC RHINITIS (HAY-FEVER, ROSE COLD, ETC.).

SYNONYMS.—*Hay Asthma; June Cold; Catarrhus Æstivus; Idiosyncratic Coryza; Peach Cold; Pollen Catarrh; Ragweed Fever; Summer Catarrh; etc.*

To eliminate the array of absurd names which have been given this disease, some of which appear in the above list, I suggested in 1885 the term "Hyperæsthetic Rhinitis" as best typifying its salient phenomenon: extreme sensitiveness of the upper respiratory tract. As I will show in the following pages, this term, which has been adopted by several authorities, is fully justified. Hence its appearance at the head of this article.

Definition.—Hyperæsthetic rhinitis, a periodical acute coryza often accompanied by asthma, is due to excessive irritability of the trigeminal center, a condition sustained by toxic wastes which are present at all times in the blood of these cases, owing to functional torpor of the adrenal system. The periodicity of the disease is due to the presence in the air, at fixed seasons, of certain pollens, which, coming into contact with the hyperæsthetic terminals of the trigeminus in the nasal mucosa, provoke the attack.*

Symptoms.—The affection presents itself at periodic yearly intervals, either in August and early September, or else in the months of May or June. In some individuals two attacks occur in the year. The subject is often able to state the day and even

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**Author's definition.*

[54] Huchard: Jour. des praticiens, Feb. 22, 1896.
[55] Thorowgood: Med. Press and Circular, Dec. 16, 1896.

the hour at which the onset is to occur. The summer variety of the affection is in general less severe and of shorter duration than the autumnal variety.

In some cases, mainly those of long standing, premonitory symptoms appear several days or even two weeks before the true onset. They may include general malaise, frontal headache, itching at the roof of the mouth and eyes, sensations of chilliness, and slight fits of sneezing. The symptoms of the actual attack *may last only a few days, and resemble those of an ordinary cold in the head, or may be of more violent form, and are sometimes accompanied by asthma.*

A sensation of violent itching in the nose generally marks the onset of the affection, and causes prolonged sneezing. With this may be associated pricking and stinging at and near the inner canthi, followed by profuse lachrymation. An abundant, watery, and alkaline discharge from the nose soon appears, which causes more or less irritation of the nostrils and upper lip. Respiration through the nose becomes much impeded through swelling of the nasal mucous membrane. Pain is present over the bridge of the nose; there is often also frontal headache, and pains in the eyeball or back of the head. Itching at the roof of the mouth and on the face is often complained of. Other possible manifestations comprise chilly sensations, loss of smell and taste, tinnitus aurium, partial deafness, involvement of the air-sinuses, pharyngitis, hyperæsthesia of the scalp; as well as general symptoms, such as moderate pyrexia, disordered stomach and flatulence, urticaria, with inability to perform mental work.

As the affection progresses, the nasal discharge becomes thicker in character, and may be muco-purulent. Photophobia and chemosis are prone to develop, and, occasionally, pseudomembrane is formed in the nasal cavities. The attack may last from several days to as long as a few weeks, and when left untreated does not tend to disappear until the constituent of the atmosphere that causes the irritation is removed. Usually both onset and decline of the symptoms are sudden, but in some cases they may be more gradual.

Asthma not infrequently occurs as a complication of hay-fever. In most cases it begins a few days after the primary nasal symptoms have appeared and as soon as these become marked. There comes a feeling of soreness in the pharynx, which is soon followed by hoarseness, slight cough, and a sense of tightness about the chest. These symptoms gradually increase in intensity and are generally worse at night. Sometimes they cease with the nasal symptoms, but in many other cases last for weeks or even months after the catarrhal attack.

Etiology and Pathogenesis.—The predisposing cause of hay-fever is an excessive irritability of the trigeminal center in the pituitary body, due to the presence in the blood of toxic waste-products.[*] The presence of these toxic wastes is in turn the result of hypoactivity of the adrenal system, a condition which may be either inherited or brought on by diseases of an adynamic type, especially those of childhood.[*] The proportion of adrenoxidase formed being inadequate, catabolism is carried on imperfectly and the intermediate wastes that are constantly present in the blood sustain the hypersensitiveness of the trigeminal center.[*]

As a result of this trigeminal oversensitiveness,[*] the mucous membranes, particularly those nearest the pituitary body,[*] *i.e.*, the nose (when the seat of local lesions, hypertrophies, polypi, exostoses, etc., especially), the eyes, pharynx, ear, and in some cases the entire respiratory tract, are hyperæsthetic. Some patients show evidence of this condition by fits of paroxysmal sneezing throughout the year, under the influence of certain irritants, emanations, etc., others only at fixed periods, when certain pollens are present in the air breathed. The patients of the latter category constitute the cases of "rose-cold" that occur in May or June, and those of "hay-fever" that occur, as a rule, in August.

That hay-fever is a neurosis was first shown by George W. Beard, of New York, in 1876, while the rôle of pollen as the most frequent exciting factor was demonstrated the following year by Elias Marsh, of New Jersey. That lesions, growths, polypi, etc., play an important part in the pathogenesis of some cases, was demonstrated by W. H. Daly, of Pittsburg, in 1882, and in 1884 by Harrison Allen. All these features of the problem have been sustained by a large number of investigators.

The identity of the underlying cause of the disease, a general adynamia, was demonstrated by myself in 1885[38] after a study of 40 cases. Of these, nineteen showed a clear history of inherited predisposition to hay-fever, asthma, etc., while the rest had been rendered

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[*] *Author's conclusion.*

[38] Sajous: "Lectures on the Diseases of the Nose and Throat," p. 170, 1885.

vulnerable by a large number of diseases of childhood: 55 per cent. having had six of these diseases, and 85 per cent. four of them. This view was independently sustained by Joal,[57] Cartas[58] and others. Fink[59] *holds that "the patient is always neurasthenic."*

The ubiquitous result of such adynamia, *i.e.*, defective metabolism, as manifested by the "arthritisme" of French authors or our "gouty diathesis," has been noted by many observers since Guéneau and Mussy (1868) suggested it. Leflaive[60] having found that the uric acid ratio of the urine before and after attacks corresponded with that of gout, also ascribed the disease to the "gouty diathesis." Bishop, of Chicago, also urged this view in 1893. Grube[61] emphasized the fact that "most cases are among patients having gout or of gouty tendency, or with a history of gout in the family."

The next factor, the hyperæsthesia of the nasal and other mucous membranes, was first urged by John O. Roe, of Rochester, in 1883, and in 1884 by J. N. Mackenzie, of Baltimore, and others, the last-named observer concluding that there was also "a hyperæsthetic state of (probably) the vasomotor centers." The presence of "sensitive areas" in the nose may in fact be readily discerned with the aid of a probe, and has formed the basis of remedial measures.

The pathogenesis I submit in the general text coincides, therefore, with all the strongest doctrines that have been advanced, and—a suggestive fact—harmonizes them all. As to the rôle of the pituitary body—which contains, according to my views, the chief trigeminal center in the process—Cyon, we have seen, found that the nasal mucous membrane at once lost its usual sensitiveness (which, on irritation, provokes sneezing, lachrymation, etc.) after the pituitary was removed, and that even the most active stimulants, ammonia, for example, failed to elicit the least response."

Treatment.—PROPHYLACTIC MEASURES.—The constitutional factor of the disease is obviously of major importance in this connection, the object being to diminish, by a judicious diet, the toxic wastes which sustain the hypersensitiveness of the trigeminal center.* The nearer the indications for gouty subjects are followed, the better the patient fares. The reader is referred to the treatment of gout[62] for the prophylactic measures indicated.

Of equal importance is a thorough examination of the nasal cavities and the correction of any deformity which, when the mucous membrane is slightly engorged and swollen, causes opposite surfaces to meet. Polypi are not infrequently found in hay-fever cases; their removal alone affords marked relief; this applies likewise to sharp exostoses. On the whole, any disorder of the nasal cavities tends to aggravate the hyperæsthesia, and should be removed. If the probe passed gently over the nasal mucous membrane indicates the presence of areas that are exquisitely sensitive, their cauterization by the electric cautery or acids tends greatly to prevent the attack, especially if done within two or three weeks before the periodical onset.

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* *Author's conclusion.*

[57] Joal: Revue de laryn., otol., et rhin., vol. xv, pp. 273, 325, 1895.

[58] Cartas: Thèse de Paris, 1895.

[59] Fink: Therap. Monats., Bd. xviii, S. 175, 1904.

[60] Leflaive: Gaz. des hôpitaux, vol. lxi, p. 329, 1888.

[61] Grube: Lancet, July 7, 1900.

[62] *Cf.* this volume, p. 1514.

As to preventive remedies, those which provoke destruction of all toxic wastes are the most beneficial, since they rid the blood of the cause of the trigeminal irritant.* The best of these is *thyroid gland,* 2 grains (0.13 gm.), three times a day (during meals) in adults, reduced after the fourth day to 1 grain (0.06 gm.), thrice daily.* This should be begun about four weeks before the onset of the periodical paroxysm.* *Strychnine,* in doses of $^1/_{40}$ to $^1/_{20}$ grain (0.0016 to 0.003 gm.), is also beneficial in some cases when the arterial pressure is low. *Digitaline,* in doses of from $^1/_{20}$ to $^1/_{10}$ grain (0.003 to 0.0065 gm.), during breakfast and supper, is indicated when there is simple cardiac dilation owing to general adynamia.* *Atropine,* in $^1/_{100}$ grain (0.00065 gm.) granules, night and morning, by enhancing the propulsive activity of the arterioles, increases the nutrition of the nerve-centers, including those of the pituitary body,* but its action on the pupil renders it an objectionable remedy. *Quinine hydrochlorate,* 3 grains (0.2 gm.), after meals, fulfills the same object by causing a rise of the blood-pressure.* The effects of these two remedies are ephemeral, however, and the first three are much to be preferred.

An important feature of the paroxysmal period as well as of the paroxysm itself, is to counteract acidosis, or what might be termed "ammoniosis," an excess of ammonia—an intermediate waste in this connection. This is readily accomplished by the use of *Vichy water* as a beverage, a quart being taken during the twenty-four hours.* The osmotic properties of the body fluids are thus preserved, and the elimination of wastes by the urine, intestine and sweat is facilitated. The same end is attained by drinking daily a quart of spring water containing one teaspoonful of *sodium chloride* and a similar quantity of *sodium bicarbonate.**

Strychnine, atropine and quinine have been used and recommended by others; I do not find evidence to the effect that thyroid extract or digitalin have been used so far, except by myself. In suitable cases and when the dietetic measures recommended were carried out faithfully by the patient, they gave the best results.

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* *Author's conclusion.*

The importance of acidity or excessive alkalinity of the nasal secretions in the pathogenesis of the disease, was first shown by D. Braden Kyle, of Philadelphia,[**] who writes in this connection: "That the chemistry of the secretions has to do with the causal factor, I have illustrated in a number of cases by rapidly changing the reaction of the secretion either from acid to alkaline or alkaline to acid, or rendering it neutral, and in many instances I have been able either partially or wholly to cure the attack." The author holds, moreover, that in a certain proportion of cases, the ammoniacal salts eliminated by the nasal mucous membrane act as irritants—sufficiently so in fact to bring on an attack. There is doubtless considerable truth in this view, since, as I have shown in the preceding articles, bronchitis and bronchial asthma are caused by a vicarious elimination of toxic wastes through the bronchial mucosa. That these ammoniacal salts are wastes is evident. Allantoin, which results from the oxidation of uric acid by potassium permanganate, for example, is an ammonia derivative; we not only have the uric acid in the blood-plasma of these cases, but also the counterpart of potassium permanganate as a powerful oxidizing agent, viz.: adrenoxidase.

AGENTS INDICATED DURING THE ATTACK.—The paroxysm being brought on reflexly by irritants in contact with the mucosa of the upper respiratory tract, the morbid process is as follows: Sensory impulses are transmitted to the trigeminal center of the posterior pituitary; this center being hypersensitive, the stricto-dilator impulses it transmits to the vasa vasorum of the arterioles of the mucous membranes are so energetic that these vessels are held widely dilated, thus causing intense congestion of the sinuses of the nasal mucosa and of the capillaries of the neighboring organs—the exciting cause of the distressing symptoms.[*]

The physiological indication, therefore, is to provoke constriction of the arterioles by means of agents which excite the sympathetic center sufficiently to enforce it.[*] This may be done by means of *opium, acetanilid, antipyrin*. or any of the analgesics, in fact, since it is by causing constriction of the arterioles that they relieve pain.[*] *Codeine* is the safest of the opiates, and may be given in doses of $^1/_4$ grain (0.016 gm.), four times in the twenty-four hours. Acetanilid, in 5-grain (0.3 gm.) doses, may be given three times daily, ceasing if there is any tendency to cyanosis.

The best effects are obtained by using simultaneously vasomotor depressants and sympathetic stimulants.* The first of these, by relaxing all arteries, deplete the peripheral capillaries —including the sinuses of the nasal mucosa—and thus facilitate constriction of the arterioles by the second class of agents.* The coal-tar products become dangerous under these conditions; but *codeine* and *atropine*, which constrict the arterioles when they are dilated, are not, given as stated above; to depress the vasomotor, *sodium bromide* and *chloral hydrate*, 10 grains (0.6 gm.) each on retiring, or, if the patient is rendered sleepy in the day time, *veratrum viride*, 10 drops (1905 U. S. P.) of Norwood's tincture, may be used instead.

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[*] *Author's conclusion.*

[**] D. Braden Kyle: Laryngoscope, Sept., 1903.

Whatever remedy is used during the paroxysm, general metabolism should be sustained, avoiding drugs such as strychnine and digitalis, which increase the vascular tension. *Thyroid extract*, 2 grains (0.13 gm.) twice daily, is the best agent at our disposal.* *Adrenal substance*, 5 grains (0.3 gm.) every three hours, has been recommended by several observers.

The adrenal substance was found useful by S. Solis-Cohen,[44] Beaman Douglass[45] and others. Interpreted from my standpoint, however, the action of this agent can only be ephemeral, and it is better to sustain the production of the adrenal secretion itself by means of thyroid.

Local Treatment.—The main feature is to promote contraction of the nasal sinuses and capillaries. *Cocaine*, if used at all, should be applied by the physician only, a spray of a 10-per-cent. solution being very efficacious. A better and safer agent is *adrenalin chloride*, but only when a weak solution, 1 in 10,000, is used, stronger solutions causing such violent constriction of the arterioles that they become exhausted and markedly relaxed* when the reaction occurs, aggravating the trouble. The *adrenalin ointment* 1 : 1000 does not present this drawback, and promptly reduces the swelling of the mucosa.

To protect the nasal surface against the irritation of pollens, dust, smoke, etc., a solution of *menthol* in fluid albolene, 10 grains (0.6 gm.) to the ounce, may be sprayed over the mucosa after using the adrenalin solution. It tends also to perpetuate the effect of the latter.

Dunbar's "pollantin" cannot be taken up in this connection, since I have no data upon which its physiological action can be based. The

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* *Author's conclusion.*

[44] S. Solis-Cohen: Phila. Med. Jour., Aug. 13, 1898.

[45] Beaman Douglass: N. Y. Med. Jour., May 12, 1900.

results have been excellent according to some, and practically nil in the hands of others. Prausnitz[**] states that Dunbar's work has proven beyond doubt that hay-fever is due to the pollen of graminaceæ, which float in the air in enormous quantities during the hay-fever season. The toxin is probably of proteid character. It is likely, according to Prausnitz, that the antitoxin of Dunbar acts by causing an actual diminution of the toxins.

Hurry and excitement tend to enhance the trouble by causing an accumulation of toxic wastes in the blood. Another factor which tends to aggravate the central hypersensitiveness is bright light; hence the comfort afforded by dark glasses.

PERTUSSIS.

SYNONYM.—*Whooping-cough.*

Definition.—Pertussis is an infectious disease characterized by a violent reflex cough, due to irritation of the vagal sensory terminals in the mucous membrane of the respiratory tract by a specific germ of unknown identity.[*]

Symptoms.—After a period of incubation of from four days to two weeks, a coryza and cough appears which soon assumes a paroxysmal character. The cough is dry, short and forcible—the face becoming highly congested and cyanotic, the eyes suffused, the eyelids puffed up, etc.—and lasts until the chest is practically depleted of air. This is followed by the characteristic symptom of the disease, the "whoop," due to unusually vigorous inspiration. A clear, viscid mucus is then brought up, often accompanied by emesis of the contents of the stomach, and by involuntary micturition and defecation. Several of such attacks may follow in rapid succession, the child becoming livid and falling exhausted, and the pulse being extremely feeble and rapid. Such attacks occur from six to fifty times a day and most frequently at night. After a couple of weeks, the severity of the attacks lessens and they occur less frequently.

In most cases the general condition of the child remains relatively good; in others, the attacks are so severe that hæmorrhages occur in the conjunctiva, eyelids, brain, etc. Among other complications witnessed are broncho-pneumonia, emphysema and nephritis, various forms of paralysis, and convulsions.

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[*] *Author's definition.*

[**] Prausnitz: Berl. klin. Woch., Bd. xlii, S. 227, 1905.

Etiology and Pathogenesis.—Pertussis is due to the presence upon the mucous membrane of the respiratory tract of an organism of unidentified nature (though probably Bordet and Gengou's recently discovered organism) which, owing to the irritating character of its toxin or endotoxin, causes violent local irritation and reflex cough.* As all coughs are due to impulses transmitted by the vagal center in the posterior pituitary,* it is this center upon which the brunt of the disease falls.*

The complications are not due to the pathogenic element itself, but to the violence of the muscular phenomena, skeletal and vascular: the emphysema is due to the centripetal pressure of the air, the paralysis to cerebral thrombi, the cardiac dilation to the intense blood-pressure,* etc.

There is a certain amount of absorption of the toxin since there occurs a protective reaction, as shown by the rise of temperature (100° to 101° F.—37.7° to 38.3° C.) and the marked leucocytosis—both of which indicate that the adrenal system is hyperactive.*

The association of pertussis with irritation of various parts of the respiratory tract has been suggested by a number of observers. Ritter,[67] for instance, ascribed it to what he termed the "diplococcus tussis convulsivæ;" Arnheim[68] to a bacillus resembling that of influenza, first described by Czaplewski, found in patches throughout the respiratory tract—the identical areas which Nothnagel and Kohts had described as "cough areas." In common with all other investigators, Burman considers these hyperæsthetic areas as the sensory terminals of the vagi. The minute bacterium recently discovered by Bordet and Gengou,[69] which differs from those of Afanassieff, Czaplewski, Manicatide, Vincenzi and others, proved extremely irritating when applied locally. Injected into the eye of a dog, it caused the cornea to become white and opaque, showing, according to Bordet and Gengou, that the organism probably excreted necrotizing toxins.

That the adrenal system is overactive during the disease is not only shown, as stated, by the febrile reaction, but also by the leucocytosis which, as stated by Churchill,[70] is present in almost all cases. Grulee and Phemister[71] found that it ranged from 12,500 to 48,500 in a series of fifteen cases studied by them.

Treatment.—TO INCREASE THE BACTERICIDAL ACTIVITY OF THE SECRETIONS of the respiratory tract is of first indication. *Quinine*, in large doses, 15 to 20 grains (1 to 1.3 gm.) daily, doubtless owes its value to the fact that by stimulating the adrenal system and the sympathetic center, it increases the propulsive activity of the arterioles and thus augments the proportion of blood rich in auto-antitoxin into all capillaries, including those of the mucosa of the respiratory tract and its secretions.[*] *Belladonna* is likewise a favorite remedy, $^1/_6$ to $^1/_2$ grain (0.01 to 0.03 gm.), according to the age of the child, being given three times daily. Its action is similar to that of quinine, as to the arterioles.[*] *Creosote carbonate* in 3- to 10-grain (0.2 to 0.6 gm.) doses thrice daily, is an efficient remedy which also augments the auto-antitoxin in the blood, and dilates the arterioles, thus admitting also a larger proportion of blood into the mucosa and its secreting elements.[*] Creosote has been found useful when inhaled, and may be advantageously employed in this manner while the carbonate is given internally.

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* *Author's conclusion.*

[67] Ritter: *Ibid.*, Bd. xxxiii, S. 1040, 1069, 1896.

[68] Arnheim: Virchow's Archiv, Bd. clxxiv, S. 530, 1903.

[69] Bordet and Gengou: Le scalpel, Sept. 2, 1906.

[70] Churchill: Jour. Amer. Med. Assoc., May 19, 1906.

[71] Grulee and Phemister: Archives of Pediatrics, Aug., 1905.

All these remedies, excepting the creosote carbonate, are familiar to all clinicians in this connection, and are only mentioned to indicate their physiological action according to my views. Kerley,[72] in a comparative study of 752 cases, found quinine in large doses the most effective agent among those mentioned above. Tyrrell[73] also regards it as our best remedy; he uses the hydrochlorate.

Drugs which Reduce the Sensitiveness of the Mucous Membranes are useful to reduce the number of paroxysms. *Antipyrin*, which has been found useful, insures this effect by causing constriction of the arterioles;[*] it is given in 1-grain (0.065 gm.) doses for each year of the child's age (the maximum being 4 grains [0.25 gm.]), three times daily. *Acetanilid* is preferable in that it does not tend to cause cyanosis as readily. The *sodium* or *potassium bromide* accomplishes the same object in a different way, viz., by depressing the vasomotor center and causing the blood to recede from the peripheral capillaries.[*] *Chloral hydrate* produces a similar effect[*] and is useful at night to prevent the nocturnal paroxysms.

These remedies give the pathogenic germ free sway, however.[*] Their pullulation should be antagonized, therefore, by antiseptic sprays or steam, using a 5 to 1000 solution of carbolic acid, 10 to 1000 solution of resorcin, a 1 to 5000 of corrosive sublimate, or better, the creosote inhalations previously referred to.

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[*] *Author's conclusion.*
[72] Kerley: Pediatrics, May 1, 1903.
[73] Tyrrell: Medical Record, July 22, 1905.

A very efficient measure as a derivative is the application of hot poultices to the back of the lungs, and the use of a wide belt to constrict the abdomen and sustain it during the paroxysms.

The hot poultices recommended by J. Madison Taylor have been found of considerable value by McKee[74] and others. The poultice is made large enough to cover the posterior surface of the lungs, and on this the child is permitted to lie for one hour without change. Relief is almost immediate. An excellent belt is that devised by Kilmer[75] and sold by Jungmann of New York.

Fresh air and out-of-door life are as beneficial in cases of pertussis as they are in tuberculosis. Dust, smoke, tobacco smoke, etc., greatly aggravate the irritation of the respiratory surfaces and increase the paroxysms. The child should be dressed warmly, and should, as much as possible, not be allowed to become excited.

To shorten the accesses, Taylor's combination of three parts of *chloroform*, five parts of *ether*, and one-half to one part of *amyl nitrite*, is very effective. A few drops of the mixture are applied on a handkerchief and held under the nose. The last-named remedy is the main factor in the effect produced, acting as it does by relaxing the excessive vascular tension.

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[74] McKee: Phila. Polyclinic, Sept. 14, 1895.
[75] Kilmer: Archives of Pediatrics, Feb., 1907.

CHAPTER XXX.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

THE ADRENAL SYSTEM IN THE DISEASES OF THE ALIMENTARY CANAL.

The series of diseases embodied in the present chapter is intended to illustrate three salient facts: (1) the cardinal rôle which the intestinal canal fulfills in the defence of the body at large against infection by increasing, when necessary, the proportion of auto-antitoxin in the intestinal juice; (2) that certain toxins, endotoxins or other poisons can depress and even paralyze the vasomotor and sympathetic centers precisely as is the case with depressing drugs; and (3) the fact that the *deprivation of auto-antitoxin* which maternal, or at least breast-milk, entails when infants are hand-fed accounts for the fatality of intestinal diseases among them besides, as already shown in the preceding chapter, rendering them highly vulnerable to infection.

CHOLERA ASIATICA.

SYNONYMS.—*Epidemic Cholera; Cholera Algida; Cholera Maligna.*

Definition.—Asiatic cholera, an infectious disease caused by Koch's comma bacillus, is due to paresis of the test-organ and the vasomotor and sympathetic centers by the endotoxin of this pathogenic organism.*

Symptoms.—After an incubation period varying from two to five days, the disease sets in by a *premonitory diarrhœa* often accompanied by slight colicky pain and borborygmus. The patient feels well otherwise. After a period varying from a few hours to a few days, however, he becomes weak, experiences fleeting cramps in the extremities and chills, and, perhaps, vertigo or faintness. This is accompanied by a change in the character of the stools.

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* *Author's definition.*

This introduces the stage of *serous diarrhœa*, in which the stools, from fæcal or bilious, become fluid and serous, devoid of fæcal odor and laden with rice-like flakes, thus constituting the "rice-water" stools. Several of these stools, each representing a large quantity of blood-serum, may be passed without pain, but soon abdominal cramps are experienced and vomiting sets in—also of "rice-water"—accompanied by a feeling of intense exhaustion. Gradually as the loss of serum increases, thirst becomes greater, until it is intense and insatiable, and the urine becomes scanty or absent. The face is at first pale, but it soon assumes a leaden hue. As the flux increases, the patient grows steadily weaker, the pulse being small, weak and rapid, and in some cases irregular. The muscular cramps may also become severe and the extremities cold. This may prove to be but an attack of "choleraic diarrhœa" or "cholerine," often met with during cholera epidemics. If this be the case, the symptoms gradually improve and the patient finally recovers. On the other hand, collapse may occur more or less suddenly, followed by death. Such a case may last from six hours to two days.

If the case prove to be one of true cholera, it lapses into the *algid stage*. As described by a clinician who has observed many such cases, "this is announced by a lessened frequency and abundance of the dejections, which sometimes cease altogether. In a few hours, however, the patient's condition grows rapidly worse; the countenance is altered—the cheeks become hollow, the eyes sink deeper in the sockets, are encircled by a black ring; there are pains in the head, ear-tinglings, dizziness and blurred vision; the voice becomes hoarse and is soon extinguished. A feeling of anxiety assails the patient, who suffers from the most excruciating vomiting, hiccough and cramps in the calves. Cooling of the surface increases, all external parts being, as it were, frozen; but the patient feels an internal, very troublesome heat, explained by the fact that the temperature of the skin, mouth, etc., is much lowered, while that of the internal organs is raised and even febrile. At the same time the skin takes a bluish tinge with black marble-like veins coursing over the hands, feet, penis, and with increasing cyanotic dark hue of the nails. The pulse becomes weaker and smaller, until it disappears, first from the radial arteries and then from the crurals and even the carotids, while the heart-beats gradually disappear, the sounds becoming weaker until finally only the second sound is heard. To this, great emaciation is added, the body growing thin and the skin wrinkled. Breathing is frequent and difficult; every secretion is dried up, with the exception of that of the sudoriferous glands, a cold and clammy sweat covering the cutaneous surface. At the end of this stage the patient becomes extremely apathetic and somnolent, loses consciousness, slowly turning his eyes toward a person speaking to him, and at times answering some words with great fatigue, but immediately falling again into stupor. A period of agitation, during which the patient tries to rise and utter vague words, sometimes precedes this stage of collapse, which generally —in more than three-fourths of all the cases—grows worse, and ends in death. The whole duration of the algid stage is from a few hours to two or three days."

When the patient survives the algid stage, the *reaction stage* begins, *i.e.*, general improvement of all the symptoms and after a few days convalescence. In some cases, however, several of the symptoms persist, the anuria, hypothermia, dyspnœa, etc., and the patient may suffer a relapse which may prove fatal. In others, again, symptoms recalling those of typhoid fever occur—the so-called "cholera-typhoid," attended by delirium, a dry tongue, etc. This also may terminate fatally. Finally, the convalescence may be protracted and be attended by various *complications* which include many forms of cutaneous eruption, gastro-intestinal disorders, inflammatory disorders of the throat, lungs and brain, cerebral softening, insanity, tetany, palsies, etc.

Various clinical types occur, but they differ mainly through the intensity of the symptoms. Thus *cholera siderans,* observed sometimes in India, may run its course in a few hours, and in rare cases in a few minutes. Again, there are cases in which there is no diarrhœa, the so-called *dry cholera,* the absence of flux being due merely to the fact that the fluids accumulate in the intestine, because paralysis of the latter prevents their expulsion.

The clinician referred to in the text is Professor Rubino, of Naples.[1] He clearly defines in his description of the algid stage several features which are of special importance when interpreted from my standpoint.

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[1] Rubino: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. ii, p. 210, 1898.

Pathogenesis and Pathology.—Asiatic cholera is due to poisoning by an endotoxin contained in Koch's comma bacillus, which is liberated after death and disintegration of this micro-organism. Although infection occurs through the alimentary canal, even large quantities of specific bactéria may be ingested and be found in the stools without causing the disease, provided the functional efficiency of the body's auto-protective mechanism be perfect.[*] Children are vulnerable to cholera because this mechanism is not fully developed; the aged are vulnerable because it has become weakened in them, as it does under the influence of any debilitating condition, ill-health, overwork, alcoholism, deficient food, etc., all of which also predispose to the disease.[*]

The gastric juice does not afford protection against water-borne cholera bacilli as believed by some. The main protective influence is exercised by the auto-antitoxin of the intestinal juice.[*]

It is now generally recognized that the poison is an *endotoxin* freed only by death and disintegration of the germ. Pfeiffer[2] found this poison intensely toxic. Cantani and Gamaleia[3] and others have made similar observations. Its identity is not established, however, but, as shown by Nicati and Rietsch,[4] Van Ermengem,[5] Koch, Pfeiffer and other investigators, the injection of pure culture of the bacillus into the intestine or the peritoneal cavity of animals evokes pathological changes and symptoms similar to those observed in cholera Asiatica: marked weakness, feebleness of the heart's action, marked coldness of the head and extremities, etc. Moreover, Koch's bacillus is always found in the stools of cases of Asiatic cholera, and in this disease *only*. Pettenkofer and Emmerich, Hasterlik[6] and others, however, as is well known, not only swallowed without evil results large quantities of cholera cultures, but as shown below, various observers have found that normal stools may contain virulent cholera vibrios though the patient show no sign whatever at the time or subsequently of cholera. That it is only under certain predisposing conditions, therefore, that the disease can develop, is obvious. As stated by Tyson,[7] "general ill-health, fatigue, the alcoholic habit, depression of spirits, fright or anxiety, any one or all may be predisposing causes. All ages and sexes are liable to be infected, but young children seem most vulnerable," and, I would add, aged people, the poor and ill-fed likewise.

When, therefore, emigrants, pilgrims, etc., coming from regions in which the disease is always endemic, as it is on the borders of the

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[*] *Author's conclusion.*

[2] Pfeiffer: Zeit. f. Hyg. u. Infects., Bd. xi, S. 393, 1891.

[3] Cantani: Cited by Gamaleia: Arch. de méd. expér. et d'anat. path., vol. iv, p. 173, 1892.

[4] Nicati and Rietsch: Arch. de physiol. norm. et path., 3 série, T. vi, p. 73, 1885.

[5] Van Ermengem: Bull. de l'Acad. roy. de méd. de Belge, 3 série, T. xviii, p. 1221, 1884.

[6] Hasterlik: Wiener klin. Woch., Bd. vi, S. 167, 1893.

[7] Tyson: "Practice of Medicine," third edition, p. 92, 1903.

Ganges, into communities containing such debilitated subjects, especially when the local hygienic conditions are defective, they communicate it to them indirectly, *i.e.*, through the intermediary of the soil, the water and the food which they contaminate with their germ-laden discharges, their soiled linen, etc. Rubino[8] writes in this connection: "Cholera vibrios can live only for a short time in fæcal matter, seldom longer than two or three days;" . . . "they live, on the contrary, very long in the soil, especially when they find in it a proper nutritious material; it seems rather that their virulence is then heightened, the elaboration of their poison becoming more rapid and intense. They can live also on the outer surface of fruits and vegetables (the duration being then from one to six days), and even on the cut surface of these, where their life may last for a time ranging from one hour (on very acid fruits) to two weeks. Cholera vibrios can grow freely in water, especially when it is stagnant and polluted with organic matter." This emphasizes the fact that infection occurs in predisposed individuals mainly through the alimentary canal, when the *true* cholera vibrio, Koch's comma bacillus, is present.

The first citadel of the alimentary canal, the stomach, is thought by some observers to protect the body through the bacteriolytic action of its gastric juice. Schultz-Schultzenstein[9] found that water containing pepsin and traces of acid killed the vibrio if .019 per cent. of hydrochloric acid is present, and that in 75 per cent. of his experimental cases 600 c.c. water ingested on an empty stomach became bacteriolytic, *i.e.*, it acquired an acidity of 0.03 per cent. In the remaining 25 per cent., however, it was only .0142 per cent.—a solution which does not kill the vibrio even in *one and one-half hours*. Now Howell[10] states that, as shown by von Mering, water introduced into the stomach begins *at once* to pass out into the intestine; and moreover, that when 500 c.c. of water were given to a large dog, by the mouth, 495 c.c. had passed into the duodenum, and out through a fistula in the latter, within *twenty-five minutes*. It is evident, therefore, that contaminated water carries the pathogenic organism directly to the intestine in at least 25 per cent. of all exposed individuals. The gastric juice does not even protect those in perfect health, since, as already stated, various investigators have found bacilli in normal stools in individuals who never developed the disease. The experiments of Pettenkofer and Emmerich on themselves demonstrate the same fact. An abundance of cholera vibrios having been found in their stools, their gastric secretions evidently did not kill the ingested cultures.

Conversely, it is believed that the alkaline juice of the intestine is necessary to develop the germ, and that it is a suitable culture fluid. But in the light of the evidence I have adduced to the effect that the intestinal juice is rich in trypsin, nucleo-proteid and adrenoxidase, this cannot be the case. This accounts for the fact that Klemperer[11] found in experiments on guinea-pigs, rabbits and dogs, that the normal intestine is strongly resistant to the cholera bacillus—an action which he attributed to a substance he found in the epithelial cells, *i.e.*, nucleinic acid and nuclein. This is obviously the nucleo-proteid, and as no one would deny the presence of trypsin in the intestine, nor since the labors of Pawlow, Delézenne, Camus and Gley, and others, that of enterokinase (trypsin plus adrenoxidase), the three constituents of the digestive triad which in the blood constitute the auto-antitoxin are evidently present. *It is the intestinal juice, therefore, which is the first serious barrier to infection.*

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[8] Rubino: *Loc. cit.*

[9] Schultz-Schultzenstein: Centralbl. f. Bakt., Bd. xxx, S. 785, 1901.

[10] Howell: "T. B. of Physiol.," p. 696, 1905.

[11] Klemperer: Deut. med. Woch., Bd. xx, S. 435, 1894.

If we now inquire into the cause of this, we are brought back to debility of the adrenal system, the result of the many untoward conditions grouped as "predisposing causes." The formation of adrenoxidase being deficient, the pancreas and the leucocytogenic organs are inadequately nourished, so that trypsin and nucleo-proteid are formed in insufficient quantities.

Cholera is not, as generally believed, an intestinal disease,* the symptoms referable to the alimentary canal being, in keeping with all the other characteristic symptoms, the result* of a general intoxication by the endotoxin of the coma bacillus. It is, therefore, by penetrating the intestinal walls and into the body fluids that the comma bacillus provokes the disease. As it is the function of the digestive leucocytes to ingest food-products in the intestinal canal in order to complete the digestive process and prepare the end-products for assimilation by the tissue-cells,* they ingest likewise in the intestine what bacteria happen to be present in the food. Infection occurs when this intracellular process is inadequate, *i.e.*, when the digestive leucocytes ingest living comma bacilli which they are unable to digest or even kill.*

The number of bacilli ingested by leucocytes is not a prominent feature of their inability to destroy these germs, since enormous quantities of the latter may be swallowed by a man in normal health without giving rise to the disease. The ruling factor of infection is deficiency of the digestive triad: trypsin. nucleo-proteid and adrenoxidase, both in the intestinal juice and in the digestive leucocytes, and infection occurs when the bacilli have, as a result, remained unaffected by the bacteriolytic action of these bodies.* It is not in the blood, as now believed, that the organisms proliferate;* the digestive leucocytes carry the living comma bacilli directly to the lymph-spaces, as if they had been digested and converted into tissue-cell granulations.* Being unassimilable, however, they are swept away as wastes by the torpid lymph-stream, and as lymph is practically blood-serum, and an excellent medium for their growth, they rapidly pullulate therein.* When, with the lymph current, they reach the blood and ultimately the arterial system, they are rapidly killed and disintegrated, and their endotoxin being liberated, general intoxication follows.*

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* *Author's conclusion.*

It is now believed that cholera is essentially an intestinal disease; yet, as observed by Karlinski[12] in his own case, while studying cholera in Arabia, the comma bacillus can be present in one's stools without provoking the disease. This was confirmed by Sawtschenko and Sabolotony,[13] Abel and Claussen,[14] Rumpel[15] and other observers. Hasterlik[16] repeated on himself and three others Pettenkofer's experiment, and as was the case with the latter, suffered no inconvenience, though the bacilli were found in the stools. The doses were gradually increased until one of the experimenters ingested an entire culture of a third generation. This caused abdominal pain and diarrhœa after thirty-six hours, but nothing more. As observed by Guttmann,[17] Kolle[18] and others, this was true cholera, since large quantities of bacilli were found in the dejections, and many such cases are observed during epidemics.

Again, while Pettenkofer, Emmerich, Hasterlik and his associates observed no effects after swallowing large quantities of comma bacillus cultures, Pfeiffer and Pfuhl[19] suffered moderately severe attacks of cholera after being accidentally inoculated with cultures. Deaths have also occurred from this cause. As "inoculation" means the introduction into the blood of a relatively very small number of bacilli, while enormous quantities of them were included in the cultures swallowed, it is self-evident that it must be *in the body fluids* that the proliferation occurs. Indeed, the bacilli were found in Pfeiffer's discharges for thirty-three days after the inoculation, and Thomas[20] has shown that all the symptoms and pathological lesions of cholera could be produced in rabbits by intravenous injections of pure cultures of comma bacilli obtained from cholera dejections.

Now is it in the blood, as generally believed, that the proliferation of the bacteria occurs? Bacteriologists have found that, as stated by Vincenzi,[21] "the cholera vibrio develops luxuriantly in the blood-serum of healthy animals" *in vitro, i.e.*, in serum deprived of its bacteriolytic activity by removal of its cells. This does not mean that a similar result can occur in the blood-stream, but that proliferation can take place in the *lymph*-stream. This becomes apparent when the functions of the digestive leucocytes, as I have described them, are taken into account. Interpreted from this standpoint, every leucocyte which happens to ingest one or more living bacilli in the intestinal canal becomes a source of infection, an inoculating agent, on entering the blood if *it does not* absorb in the intestinal canal a *qualitatively efficient supply of the digestive triad*, trypsin, and its activators, nucleoproteid and adrenoxidase, constituting auto-antitoxin, to kill the microorganisms.

In the light of the evidence adduced in the seventeenth chapter, the leucocytes do not deposit their end-products in the blood; they leave the blood-stream by migrating through the walls of the capillaries and deposit them in the tissue-spaces in contact with the tissue-cells. Unsuitable products, wastes, etc.—including the cholera vibrios in this condition—being of course unabsorbed by the latter, they are swept away by the lymph-stream. Now lymph being, as stated by Stewart, practically "blood deprived of its cells," *i.e.*, serum, we have in the torpid current of the lymph vessels a vast field wherein, at the ideal laboratory temperature, 37° C. (98.6° F.), the cholera vibrio can also develop "luxuriantly." As to the fact that the germs finally reach the blood, Bosc[=] found that the blood-serum of severe cases contained "an enormous quantity" of a substance which, injected into animals, produced all the typical signs of cholera and finally death. This poison was evidently derived from dead bacilli, for serum taken from the cases which furnished the poison failed to develop cultures.

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[12] Karlinski: Centralbl. f. Bakt., Bd. xv, S. 751, 1894.

[13] Sawtschenko and Sabolotony: Centralbl. f. allg. Pathol. u. pathol. Anat., Bd. iv, S. 625, 1893.

[14] Abel and Claussen: Centralbl. f. Bakt., Bd. xvii, S. 77, 1895.

[15] Rumpel: Berl. klin. Woch., Bd. xxxii, S. 73, 1895.

[16] Hasterlik: *Loc. cit.*

[17] Guttmann: Med. Press and Circular, Jan. 25, 1893.

[18] Kolle: Zeit. f. Hyg. u. Infectn., Bd. xviii, S. 42, 1894.

[19] Pfeiffer and Pfuhl: Cited in Med. Press and Circular, Sept. 5, 1894.

[20] Thomas: Arch. f. exp. Pathol. u. Pharm., Bd. xxxii, S. 38, 1893.

[21] Vincenzi: Deut. med. Woch., Bd. xix, S. 418, 1893.

While the functional debility of the adrenal system is the primary cause of the body's vulnerability to the disease because the specific organisms are thus allowed to reach the lymphatic vessels, proliferate therein and permeate the blood with their endotoxin,* the latter gives rise to the symptoms of the disease by paralyzing directly the functions of the vasomotor and sympathetic centers.

By inhibiting the functions of the vasomotor center, the cholera endotoxin causes, indirectly, dilation of all vessels of the body, and therefore accumulation of the blood in the great central vessels, particularly those of the splanchnic area.* The peripheral vessels and capillaries being deprived of a corresponding volume of circulating blood, the marked symptoms of ischæmia of various organs appear: coldness and pallor as to the skin; vertigo and faintness as to the brain; weakness and exhaustion as to the muscles; weakness and rapidity of the cardiac action, or anuria as to the kidneys; and dyspnœa as to the lungs.* Conversely, the accumulation of blood in the deep trunks* gives rise to the sensation of intense internal heat and the high rectal temperature, which may reach 104° F. (40° C.) or more.

Inhibition of the functions of the general sympathetic center by the endotoxin, coincides with the appearance of the serous diarrhœa.* As this center governs the caliber of the arterioles, its inhibition causes relaxation of all these terminal vessels and flooding of all the organs they supply.* The bulk of the blood of the body being accumulated in the greater central vessels, *i.e.*, those of the splanchnic area, however, as stated above, the effects of the sympathetic paresis become manifest only in the organs adjoining the congested region, and the vessels of which are themselves engorged through this contiguity.* As the vessels of the intestines form part of the engorged splanchnic area, their mucous membrane becomes markedly hyperæmic and the arterioles of its secreting elements being widely dilated and relaxed, the blood-serum, which forms the liquid portion of their secretion, and sometimes pure blood literally pour into the intestinal canal, forming the serous diarrhœa.* Mixed with the discharge are rice-like masses composed of desquamated epithelium, comma bacilli and leucocytes.

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* *Author's conclusion.*

[=] Bosc: Annales de l'Inst. Pasteur, vol. ix, p. 507, 1895.

Other symptoms are due to the relaxation of the arterioles, viz.: the cold sweats which occur before the blood has lost much of its serum; the abdominal muscular cramps, owing to the admission of an excess of blood-plasma and adrenoxidase into the muscular elements; the hiccough due to a similar condition of the diaphragmatic muscles; and the vomiting, partly caused by the accumulation, in the stomach, of serous fluids similar to those eliminated by the intestines.*

In the first volume[33] I showed by means of a chart that the nine cardinal symptoms of cholera were identical to those that follow removal of both adrenals in mammals. This coincidences, however, only with the corresponding, *i.e.*, the advanced stage of the disease, when the functions of the adrenals are paralyzed. Indeed, the violence of the morbid phenomena and the rapidity with which they lead to a fatal issue in some cases indicate, however, that other general centers are primarily assailed by the poison. This rapid course cannot be due to primary paresis of the adrenal center, since the disease would not in that case cause death in a few hours, or even a few minutes, as observed in some instances. Though Strehl and Weiss[34] and others have found that compression of the adrenal veins—thereby arresting the supply of adrenal secretion—caused an immediate fall of the blood-pressure, etc., it is nevertheless true that the circulation of the adrenals is not arrested even by paralysis of the adrenal center, and that the mere passage of blood through the adrenals is sufficient to sustain for some time, though inadequately, the vital process. We will see farther on, however, that arrest of the adrenal circulation finally does occur, and that this entails death.

That the vasomotor center is primarily paralyzed is shown by the early pallor, which occurs coincidently with the peripheral hypothermia and the central hyperthermia—the skin being cold while the rectal temperature is 104° F. (40° C.) or over. This points to accumulation of the blood in the great central trunks, the splanchnic area, and its normal consequence, depletion of the peripheral capillaries. This interpretation meets the teachings of experimental evidence, for Pfeiffer,[35] basing his opinion on the effects of dead bacilli on guinea-pigs, concluded that the poisons liberated acted as paralyzants to the centers governing the circulation and the temperature. It accounts also for various paradoxical phenomena that prevailing conceptions fail to elucidate. Thus Stiller,[36] during the Hamburg epidemic of 1892, observed the disappearance of a splenic swelling in each of three cases of typhoid fever when the patients were also attacked by cholera. Obviously, the splenic swelling was due to engorgement incident upon the fever, the deeper vessels being intensely contracted; as soon as the cholera poison depressed the vasomotor center and caused relaxation of these deeper vessels, the spleen was depleted; there was a simultaneous fall of the peripheral temperature to 95° F. (35° C.), and the organ resumed its normal volume. So plain also is the depletion of the peripheral vessels, that Klebs[27] was led to conclude that contraction of the arteries was a pathogenic sign of cholera.

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* *Author's conclusion.*

[33] *Cf.* vol. i, p. 773, in the first two editions.

[34] Strehl and Weiss: Arch. f. d. ges. Physiol., Bd. lxviii, S. 107, 1901.

[35] Pfeiffer: Zeit. f. Hyg. u. Infekts., Bd. xvi, S. 268, 1894.

[36] Stiller: Berl. klin. Woch., Bd. xxx, S. 181, 1893.

Conversely, as observed by Simmonds[28] in 300 autopsies at the Hamburg Hospital, there was hyperæmia of the intestinal serous membrane; so great is the engorgement of the intestinal structures at times, that blood is mixed with the glandular exudation, as noted by Gamaleia.[29] Indeed, as is well known, the passages are sometimes bloody. The large intestine is also, as stated by Rubino,[30] "extremely hyperæmic." It is not due to a direct action of the bacilli or their toxins on the intestine, since the local lesions are most pronounced late in the disease. Nor is the congestion restricted to the intestine. Rusi[31] found microscopically marked engorgement of the vessels of the female genital organs with extravasation. The cause of this is plain when we take into account the result of the vasomotor paresis, *i.e.*, accumulation of blood in the deep vessels, and particularly those of the splanchnic area.

The vasomotor paresis does not account, however, for the serous diarrhœa. We have seen that a number of familiar drugs, veratrum viride, chloral, the bromides, etc., also depress the functional activity of the vasomotor center.* In toxic doses they also cause marked peripheral hypothermia, a high central temperature, etc.—symptoms similar to those just described. Yet none of these drugs, even in toxic doses, cause the serous diarrhœa or flux; the cholera endotoxin must, therefore, provoke this symptom in another way. It cannot be ascribed to irritation of the intestinal canal by the specific microörganism; for, as we have seen, the normal stools of individuals in good health can contain virulent cholera vibrios, though no signs of the disease appear. Moreover, as shown by Denys and Sluys,[32] the comma bacillus does not alter the intestinal mucous membrane. Cholera occurring, as pointed out above, only when the immunizing properties of the digestive leucocytes and blood are deficient, and when the endotoxin of the dead germs is diffused in the blood, the flux can only be due to paresis of the center which governs the flow of plasma into the intestinal secretory elements. As the arterioles are the vessels which supply these structures with blood, the nerve-center paralyzed is the general sympathetic center. That the blood-serum should, under these conditions, flow in such quantities as practically to deplete the whole body (as shown by the shrunken condition of the latter after death) is self-evident.

Inhibition of the general vasomotor and sympathetic centers is not, however, the immediate cause of death. This is due to the fact that the loss of serum gradually causes the blood to become too viscid to circulate in the capillaries, and particularly, owing to their extreme minuteness, in those of the adrenals.

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* *Author's conclusion.*

[27] Klebs: Cited by Stiller: *Ibid.*

[28] Simmonds: Münch. med. Woch., Bd. xxxix, S. 845, 1892.

[29] Gamaleia: C. r. de la Soc. de biol., 9 série, vol. iv, p. 739, 1892.

[30] Rubino: *Loc. cit.*

[31] Rusi: Russ. Zeit. f. Geburtsh. u. Gynäk., Bd. vii, Hft. 1, 1904.

[32] Denys and Sluys: La cellule, Brussels, vol. x, No. 1, 1894.

(See colored plate opposite page 46, Vol. I.)* Hence the insatiable thirst, and the shrinking of the body as the loss of fluid increases; and, owing to gradual cessation of adrenal functions, the algidity, the cyanosis, the darkness of the blood,* and the steady decline of all vital functions, which finally cease when the physical conditions of the blood are such that the latter can no longer carry on its functions. The main cause of death which asserts itself, therefore, is the *viscidity of the plasma, which prevents its circulation in the capillaries, including those of the pituitary and adrenals.**

That it is simply to the lack of plasma, including of course its salts, that these symptoms are due, is shown not only by the highly beneficial influence of intravenous injections of saline solution, but also by the excretions and the condition of the blood. While Rubino[53] states that sodium chloride is included in the salts found in the rice-water stools, Carrieu[54] found the urine poor in chlorides during convalescence, thus showing a loss during the disease. Gradually as the patients improved the chlorides were found to increase. Moxon[55] found the blood in the great vessels and heart "remarkably viscid and tarry." Renvers[56] also found the tissues very dry and the blood greatly thickened. That such a condition of the blood should paralyze function is self-evident.

Treatment.—The primary effect of the cholera endotoxin being to depress the functions of the body's protective mechanism, the adrenal system, *adrenalin* in large doses, injected with one pint (500 cubic centimeters) of *saline solution* intravenously but very slowly is our most effective remedy.

Since I first pointed in the first edition of the present work (1903) the striking similarity of Asiatic cholera to adrenal failure, various observers Drake-Brockman (1910), Plovesana (1912), Naamé (1914)[56a] have emphasized the same kinship and have used adrenalin in saline solution, the last named author emphasizing the remarkable tolerance of these patients for the adrenal principle. Demetrescu[56b] found experimentally that the cholera toxin caused the disappearance of chromaffine substance from the adrenal medulla.

Surgeon-General Francis[57] states, referring to *calomel*, recommended by Ayres, of Hull, that Dr. Alderson in 1867 obtained a mortality 15 to 20 per cent. lower than that of his colleagues who depended upon astringents and alcohol. Calomel was also found very beneficial by Lieut. Col. F. W. A. de Fabeck of the Indian Medical Service. F. Peyre Porcher[58] recalled, at the time of the Hamburg epidemic, the treatment recommended by Calhoun also many years before, which, he says, though heroic, "obtained far superior results to those reported as far as the proportion of cured cases is concerned." The method was "calomel, 10 grains (0.6 gm.); gum camphor and tannin, each 5 grains (0.3 gm.) every half-hour or hour, as the urgency of the symptoms demanded, until the diarrhœa was checked and the secretions were restored to a healthy state." Pasalsky[39] found, however, that the tannin was useless without the calomel, and gave 10-grain (0.6 gm.) doses hourly for a few hours. Porcher used the calomel alone and astringent injections, plus mustard, to abdomen and extremities, and he states that by pursuing this plan in the premonitory stage, he did not lose a single patient. Van Hasselt[40] treated 51 cases with but fifteen deaths. He advised the immediate use of calomel, not forgetting to give hydrochloric acid at the same time. The calomel is mixed with a little water and gum powder, placing the mixture on the tongue, thus avoiding touching the teeth. The first dose is 1 gram (15 gr.) repeated several times. Even in convalescence 0.01 gram ($^1/_6$ gr.) is given hourly. Leyden[41] ascribed the better results obtained during the last Hamburg epidemic in part to the use of calomel. Many other clinicians have spoken in the same vein.

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* *Author's conclusion.*

[53] Rubino: *Loc. cit.*

[54] Carrieu: Nouveau Montpellier méd., vol. ii, pp. 788, 825, 1893.

[55] Moxon: Fagge's "Pract. of Med.," vol. i, p. 312, 1886.

[56] Renvers: Deut. med. Woch., Bd. xx, S. 53, 1894.

[56a] Naamé: Presse Médicale, vol. xxii, p. 725, 1914.

[56b] Demetrescu: Bulletin de la Section Scientif. de l'Académie Roumaine, vol. iii, p. 225, 1914-1915.

[57] Francis: Med. Press and Circular, Sept. 23, 1896.

[58] F. Peyre Porcher: Med. Record, Nov. 26, 1892.

Administered by the mouth, however, especially when the serous diarrhœa has begun, the drug is greatly exposed to being washed down the intestinal canal and thus fail to be absorbed. The effects would be rendered far more certain and prompt* by giving the *biniodide of mercury* intravenously, the quantity administered being at least $^1/_2$ grain (0.03 gm.) frequently repeated, until the stools become greenish, *i.e.*, bile-stained.* Dissolved in thirty drops of warm, sterilized water, this quantity can be injected into the veins at the bend of the elbow without causing the least pain, while reaching the test-organ within a minute.*

The fact that calomel administered by the mouth proves ineffective —for the reason suggested in the general text—has caused its use to be abandoned by many practitioners. Thus Surgeon-General Francis[42] states that "many practitioners condemn it," on the plea that "the drug lies inert in the intestine." The mode of using mercury recommended above is used in the treatment of syphilis. Of various salts of mercury used intravenously in this disease in the course of 408 injections, the biniodide was found, better than any, to meet the conditions of this procedure: perfect solubility; failing to coagulate albumin; ready sterilizability; painlessness, and rapidity of action.

Mercury not only counteracts the paralyzing influence of the cholera bacillus endotoxin on the test-organ, but it increases its functional activity, thus causing an accumulation of auto-antitoxin in the blood.* The cholera bacillus being easily destroyed by the immunizing constituents of the blood, the infection is directly antagonized.* The thyroidase being an important factor in this process as sensitizing agent (opsonin) to facilitate the bactericidal function of the phagocytes, *thyroid gland*, 10 grains (0.6 gm.), should be given at once orally, followed by 5-grain (0.3 gm.) doses every two hours.*

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* *Author's conclusion.*

[39] Pasalsky: St. Peters. Inaug. Dis., No. 24, p. 55, 1892-93; Provincial Med. Jour., Nov. 1, 1893.

[40] Van Hasselt: Sajous's "Annual of the Univ. Med. Sci.," vol. 1, D. 26, 1894.

[41] Leyden: Deut. med. Woch., Bd. xx, S. 37, 1894.

[42] Francis: *Loc. cit.*

The vulnerability of the cholera bacillus was shown by the researches, among others, of Pfeiffer and Vagedes,[43] who found that no other germ was similarly inhibited, as shown by the hanging drop. A serum employed by them (the counterpart of auto-antitoxin, as viewed from my standpoint) was diluted in fifty times its quantity of bouillon. The microscope showed the gradual inhibition of the activity of the cholera bacilli until complete inactivity of all the germs present occurred. This action is even more violent in the living serum, where the germ is not only inhibited but destroyed.

The next morbid factor to overcome is the paresis of the vascular centers, due to the direct action of the cholera endotoxin.* This is, to a certain extent, overcome by the mercury and the thyroid extract, both of which, by enhancing the functions of the adrenals, cause a general rise of the blood-pressure.* An active agent is required, however, to excite the sympathetic center, in order to cause constriction of the intestinal arterioles which are allowing the serum of the blood to escape into the intestines.* The best agent for this purpose is *morphine*, which interferes in no way with mercury and thyroid,* and also tends to relieve the suffering, which is very great.

Some theoretical objections have been raised to the use of opium, but its physiological action having remained obscure until I pointed out its action on the sympathetic center, they were devoid of foundation. Eichhorst[44] found that it gave, on the whole, the best results in the epidemic at Königsberg, and others have likewise praised it. In the light of the views submitted above, however, it should only be regarded as a valuable adjuvant, since it does not influence the protective process itself.

The curative efficiency of all these agents is greatly compromised, however, by the fact that early in the course of the disease, the blood becomes increasingly viscid until the capillary circulation is rendered practically impossible. Any amount of auto-antitoxin and any number of phagocytes which the mercury and thyroid extract may evoke become useless. Hence the overwhelming importance of *saline solution* in this disease. The great error made usually, however, is to wait until the algid stage is reached, *i.e.*, when the fatal trend has begun. It should be given intravenously at a temperature of not less than 110° F. (43.3° C.) *from the outset,** beginning with a few ounces at a sitting* and increasing to one or two quarts, if necessary, later on.

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* *Author's conclusion.*

[43] Pfeiffer and Vagedes: Centralbl. f. Bakt., Bd. xix, S. 385, 1896.

[44] Eichhorst: Corresp. f. schweizer Aerzte, Sept. 15, 1892.

The use of saline solution is another feature which was emphasised many years ago. In 1831-32 O'Shaughnessy, writes R. H. Cox,[65] "proposed to combat the *collapse* stage" of cholera "by means of intravenous injections." He also gave the following analysis of the blood: "(1) A material diminution of the water of the blood of the cholera patient, the specific gravity of the serum ranging from 1041 to 1054; (2) a notable decrease of the quantity of soluble salts, amounting, as far as regards the serum, to a mean loss of one-third of those substances; (3) that the solid constituents of the crassamentum, including its salts, retained their normal proportions, wanting merely water to restore it to the normal state; and (4) that the dejections were alkaline and albuminous, and contained the water and soluble salts in which the serum of the blood was deficient." Latta, of Edinburgh, inspired by these conclusions, "was the first to practice intravenous injection in the *collapse* stage of cholera." His object, however, adds Dr. Cox, "was not to supply oxygen to the blood, but to replace the salines and water lost from it by the purging and vomiting." In some of the moribund cases even, detailed, the results might aptly be termed resuscitations. The highest authorities, Cantani, Hayem, Huchard, Dehio, Neumann and others, have urged the great value of saline solution. Hager,[66] after using it in 967 cases in Hamburg, was led to regard it as the only remedy of value during the algid stage. Heyse[67] likewise found intravenous injections alone to give good results. Gagen-Torn,[68] after using intravenous injections of saline solution in 200 cases with a mortality of only 15 per cent., concludes that "the injections should be given as early as possible; during the stage of reaction, they are of but little use."

Other remedies are capable of exciting the adrenal system during the acute stage—those enumerated under the next heading—but none can be said to fulfill the object as perfectly as mercury and thyroid gland.

Prophylaxis.—The vulnerability to Asiatic cholera depends, in the light of my views, upon the efficiency of the adrenal system.* As this may be raised by a number of drugs which, by exciting the test-organ and through it the adreno-thyroid center, increase markedly the blood's asset in auto-antitoxin, it may be said that it is within our power to immunize ourselves during an epidemic.* *Thyroid gland* is the most active adrenal stimulant of all, and adds opsonin to the blood; it is, therefore, clearly indicated.* *Iodine* and the *iodides* are nearly as efficient;* *cocaine* is a powerful adrenal stimulant,* but the danger of the cocaine habit must not be overlooked; *belladonna* is likewise an adrenal stimulant,* but its action on vision precludes its use in sufficiently large quantities to afford protection. *Strychnine* is less effective than either of the above, though valuable for continuous use, especially with *quinine hydrochlorate**—but not in large doses as to the latter, since the leucocytes must not be endangered.

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* *Author's conclusion.*
[65] R. H. Cox: China Med. Missionary Jour., June, 1897.
[66] Hager: Deut. med. Zeitung, Jan. 4, 1894.
[67] Heyse: Deut. med. Woch., Bd. xviii, S. 1074, 1892.
[68] Gagen-Torn: Med. Obosrenie, No. 3, 1896.

Alcohol, which deoxidizes the blood, and heavy smoking (nicotine being a powerful adrenal depressant) should be avoided during a cholera epidemic,* but *coffee* is beneficial, being, like strychnine and adrenal extract, a vasomotor stimulant.*

CHOLERA MORBUS.

SYNONYMS—*Cholera Nostras; Sporadic Cholera.*

Definition.—Cholera nostras, a sporadic non-infectious disease resembling greatly Asiatic cholera, though seldom fatal, is due to marked depression of the adrenal vasomotor and sympathetic centers by certain poisons derived from decomposing foods, shell-fish, etc., and the toxins or endotoxins of certain bacteria, some of which present the characteristics of Koch's comma bacillus.**

Symptoms.—The attack usually comes on suddenly, the earliest symptoms being, as a rule, slight faintness, fleeting griping abdominal pain and nausea. These symptoms gradually grow more intense, and are finally replaced by severe cramps in the abdomen, and sometimes in the extremities, with purging and vomiting, and marked tendency to fainting. The body and particularly the face become very cold and covered with cold sweat, and the surface temperature may be reduced several degrees. There is extreme pallor, and sometimes cyanosis, the eyes being sunken and dull. The pulse becomes rapid and weak, and in severe cases may be irregular. The patient experiences a sensation of extreme illness and prostration; his sufferings are indeed very acute.

At first the vomited material is composed of what aliments may have remained in the stomach, but soon it becomes viscid and bile-like, then clear and serous. The stools also at first contain normal, though dilute, excrementitious products, but they finally become watery and may, in severe cases, present all the characteristics of the rice-water discharges of Asiatic cholera. The urine is usually scanty and may even be absent, though the patient suffers from intense thirst. This is aggravated by the fact that the salivary secretion is likewise reduced.

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* *Author's conclusion.*
** *Author's definition.*

In the majority of cases witnessed, these symptoms last from twelve to twenty-four hours, then gradually subside, leaving the patient weak and pale for a few days. It seldom proves fatal, except in very young, old, or debilitated subjects.

The choleraic diarrhœa observed in Europe and Asia includes all the above phenomena, but they come on slowly and persist several days or even weeks, collapse occurring in some instances in from four to six days. An attack of cholera morbus may be unattended by pain, as shown by a severe case reported by G. G. Speer.[29]

Pathogenesis and Pathology.—Cholera morbus is usually caused by poisons, bacterial toxins or endotoxins, including that of the comma bacillus, ptomaines or leucomains, which are ingested with beverages or decomposed foods, especially shell-fish and cheese, etc., and which the gastro-intestinal secretions and the digestive leucocytes fail to convert into benign assimilable end-products. Once in the blood they depress markedly the functions of the test-organ, *i.e.*, of the adrenal system, and those of the vasomotor and sympathetic centers.* As a result there is general relaxation of the vessels throughout the body and retrocession and accumulation of the blood in the deeper arteries, especially those of the great splanchnic area. The arterioles being simultaneously relaxed through the paresis of the sympathetic center, the glandular elements of the skin and of the alimentary canal are flooded with blood-serum, the source of the fluids which constitute their secretions.* Hence the profuse sweating, vomiting, purging and the copious serous discharge.*

At first there is considerable irritation of the gastro-intestinal mucosa. The intestinal hyperæmia witnessed, however, is not due to this enteritis, as text-books teach, but to relaxation of the vascular elements. Rubino[30] states that "the essential pathological conditions involved are a morbidly sensitive condition of the mucous membrane of the alimentary canal, a general impairment of the tonicity of tissues with deficient oxygenation of the blood, and so decided an impairment of the vasomotor nervous influence over the vessels of the mucous membranes of the stomach and intestines as to allow copious exudation of the serous elements of the blood." The morbid sensitiveness to which he refers is, in the light of my views, the result of a temporary inability on the part of the sufferer's adrenal system to adequately protect him. Excessively warm weather, fatigue, cold and damp, etc., are all conditions which debilitate the organism and thus predispose it to cholera morbus if one of the pathogenic elements happens to be ingested. This does not mean, of course, that a sufficiently large quantity of poison will not prove pathogenic to a normal subject. Many such cases are witnessed.

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* *Author's conclusion.*

[29] G. G. Speer: Amer. Medicine, Oct. 25, 1902.

[30] Rubino: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. ii, p. 242, 1898.

In some cases, irrespective of any Asiatic cholera epidemics, germs very similar to Koch's comma bacillus are found in the evacuations. Cases of this kind have been reported by Finkler and Prior, and Gilbert and Girode.[51] Talamon[52] found, in fact, the typical bacillus, and held that "cholera nostras and cholera Asiatica were one and the same disease." Deaths from cases of this kind have been reported by Style,[53] Hobbs[54] and others.

Treatment.—*Opium* almost fulfills the rôle of a specific in this disease, owing to its stimulating action on the sympathetic center.* All the peripheral arterioles being soon restored to their normal caliber, the serous effusion ceases, and the blood-pressure being raised by the restitution of the normal resistance to the blood-stream, all the nerve-centers, general and subsidiary, receive more blood and resume their normal functions.* To obtain this effect, not less than ¼ grain (0.016 gm.) of *morphine* should be administered hypodermically in an adult. The *camphorated tincture of opium,* paregoric, two to three teaspoonfuls in a half tumblerful of water, is also very efficient. These doses should be repeated if necessary. *Atropine* has been found of special value in severe cases in $^1/_{120}$-grain (0.00054 gm.) doses. It is, like morphine, a powerful stimulant of the sympathetic center,* and may be given simultaneously. *Calomel,* owing to the energy with which it stimulates the adrenal center, promptly restores the patient to his normal condition when given in $^1/_{10}$-grain (0.0065 gm.) doses every hour three or four times.

Atropine was recommended by Hueppe[55] for cases in which the signs of intoxication are severe. Waugh[56] states that symptoms of cholera morbus subside promptly after a hypodermic injection of $^1/_{134}$ grain (0.00049 gm.) of atropine, repeated if necessary. He also found

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* *Author's conclusion.*

[51] Gilbert and Girode: Le bull. méd., vol. v, p. 119, 1891.

[52] Talamon: La méd. moderne, vol. iii, p. 543, 1892.

[53] Style: Lancet, Aug. 28, 1897.

[54] Hobbs: La sémaine méd., vol. xvii, p. 437, 1897.

[55] Hueppe: Sajous's "Annual," vol. i, D., p. 25, 1891.

[56] Waugh: Medical Council, Aug., 1903.

$^1/_{20}$ grain (0.0033 gm.) of calomel every fifteen minutes very efficient. Most authors recommend hot aromatics, ginger, capsicum, etc. Others mention nitroglycerin among the agents tried—in vain, of course. That all drugs capable of still further increasing the vasodilation should be avoided is self-evident.

In severe cases the great loss of fluids causes the blood to become viscid, and to lose much of its plasmatic saline constituents; its osmotic properties are therefore greatly impaired, and life is endangered. Intravenous injections of *saline solution* act promptly under these conditions; three to four pints—each pint containing one teaspoonful of common salt—may be injected at a sitting.

A number of cases have been reported in which this measure actually saved life. In a case reported by John Callan[37] all the standard remedies, including morphine and belladonna, had been tried in vain. When the patient had about become pulseless and his temperature had fallen to 95.5° F. (35.3° C.), three pints of saline solution at 106° F. (41.1° C.) were injected into the median cephalic vein. Consciousness returned before the third pint had been used, and the pulse was soon beating normally.

CHOLERA INFANTUM.

SYNONYMS.—*Infantile Cholera; Acute Catarrhal Enteritis.*

Definition.—Cholera infantum, a comparatively rare form of infantile diarrhœa which symptomatically closely resembles Asiatic cholera, is due to paresis of the adrenal, vasomotor, and sympathetic centers by various kinds of poisons, especially those ingested with or formed in milk. It is usually met with in hand-fed infants.*

Symptoms.—After a period of restlessness and perhaps a slight diarrhœa with some abdominal pain, the child begins to vomit and purge with steadily increasing frequency. The temperature rises, but in the rectum only, where it may ultimately reach 105° F. (40.5° C.), the skin being cold and clammy—a condition recalling the algid stage of Asiatic cholera. The pulse is weak and rapid; the respiration is irregular or of the Cheyne-Stokes type. The infant fairly fades away, its weight and strength decreasing rapidly and its fontanelles becoming deeply depressed. It is at first very pale, then grayish, the eyes being sunken and encircled with black rings. Restlessness is marked, a fact due to abdominal and muscular cramps, the abdomen being retracted and the limbs in some cases being drawn up suddenly, then violently extended. Convulsions may occur, the head being retracted. Thirst is extreme—a symptom aggravated in some cases by the fact that all foods and liquids are vomited. The urine is scanty and sometimes suppressed. In some cases there is marked apathy, and the patient lies in a semi-comatose condition; the pupils are unequal and sluggish. The material vomited is at first composed of bile-stained mucus, but it soon becomes serous; the first stools are usually fæcal, then perhaps greenish, but finally they also become serous and exceedingly copious and exhausting.

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* *Author's definition.*

[37] John Callan: New Orleans Med. and Surg. Jour., Jan., [illegible]

Collapse may occur in from a few hours to a couple of days. The decline is marked by gradual cessation of the acute symptoms and lowering of the temperature. As the end is approaching, however, the latter may become very high—107° to 108° F. (41.6° to 42.2° C.)—and convulsions may supervene, the child then lapsing into lethal coma.

Although the mortality of cholera infantum is very large, the prognosis is not altogether hopeless. The tide may turn during the first twenty-four hours, all the symptoms gradually disappearing. Relapses are not uncommon, however, and convalescence is slow.

Pathogenesis and Pathology.—Cholera infantum is due to intoxication by various kinds of poisons, bacterial toxins and endotoxins, ptomains, leucomains, tyrotoxin, etc., ingested with, or derived from, food-stuffs. It is usually met with in hand-fed infants, and when observed in nurslings, is the result of a toxic condition of the milk due to indisposition of the nurse. The majority of cases occur during hot weather, when foods, including milk, are most apt to undergo putrefactive changes leading to the formation of poisons, or to become contaminated by dust, bacteria, flies, etc. The gastro-intestinal juices of infants being deficient in auto-antitoxin*—since the mother's milk is normally aseptic and provides her nursling with the auto-antitoxin its intestines and body require*—the intestinal poisons are absorbed.

Once in the blood, the poisons provoke, as in cholera morbus of adults, paresis of the test-organ and of the vasomotor and sympathetic centers.*

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* *Author's conclusion.*

General vasodilation being thus produced, the blood recedes from the surface to the great central vessels, the cutaneous capillaries being practically depleted.* Hence the high rectal temperature and the simultaneous coolness of the surface, which later assumes the algidity of the corresponding period of Asiatic cholera.* This symptom is aggravated by the lowered oxygenation which the paresis of the adrenal center entails.*

The gastro-intestinal flux, the most striking symptom of the disease, is due to the paresis of the sympathetic center, *i.e.*, to the resulting dilation of the arterioles they govern.* The gastro-intestinal capillaries being engorged, the blood-serum escapes in large quantities through the mucosa and is voided as soon as a sufficient amount has accumulated in the stomach or intestine. Hence the serous character of the stools.

The terminal convulsions are due to the accumulation of waste-products in the blood, owing to the lowered oxygenation.* It denotes resumption of the adrenal functions, to such a degree sometimes, that the excessive temperature referred to, 105° to 108° F. (40.5° to 42.2° C.), is brought about.* This would prove a life-saving reaction were it not for another pathological condition, viz., the viscid condition of the blood caused by the loss of serum and of the salts it contains. Its osmotic properties being greatly impaired, it can no longer penetrate the capillary walls to bathe the cellular elements and sustain life.*

Many pediatrists and bacteriologists have closely studied the bacteriology of cholera infantum, but the consensus of opinion at the present time is that it cannot be attributed to a specific bacterium. That various microörganisms may, either through their toxins or the decomposition they promote in the ingesta and other factors enumerated in the text, cause the disease, is generally recognized. As stated by Blackader,[illegible] "there are very few changes found after death either in the intestinal canal or in any of the organs"—a fact which, in view of the violence of the symptoms, relegates us to the nervous system. Indeed, the same author says in this connection: "The earlier symptoms may, therefore, reasonably be ascribed to the influence of some toxin upon the heart, nerve-centers and vasomotor nerves of the intestines, while many of the later symptoms must be referred to the great abstraction of serous fluid from the body." While this explains nothing, it points to the nervous system as an initial factor in the morbid process. Again, Tyson[illegible] writes: "The temperature should be taken in the rectum, as that of the axilla may be misleading. Indeed, the skin sometimes feels cool when the internal temperature is high." In the light of my views the axillary temperature does not mislead: it points to the actual condition—a low peripheral temperature, while that of the rectum is high. As I have explained, this is due to paresis of the vasomotor center.

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* *Author's conclusion.*

[illegible] Blackader: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. ii, p. 225, 1898.

[illegible] Tyson: *Loc. cit.*, third edition, p. 290, 1903.

Treatment.—The measures indicated in this disease depend upon the progress it has made when the infant is first seen. Powerful adrenal stimulants are required when the case is seen early; if seen late, the first indication is to restore the blood to its normal fluidity, and then to use adrenal stimulants.*

If the child is seen before the rice-water stools and algidity have begun, and the stools are still fæcal or greenish and acid, *calomel* is required, $\frac{1}{4}$ grain (0.016 gm.) being administered every twenty minutes until the stools assume a better aspect—which they usually do after five or six doses have been taken. This agent not only rids the intestines of toxic substances, but it stimulates powerfully the adrenal center. By thus causing an accumulation of auto-antitoxin in the blood, it promotes catabolism of the poison, especially in the liver. Moreover, a cardinal feature of the curative process is the fact that the increase of auto-antitoxin raises the tone of the vessels and the general blood-pressure by penetrating the muscular layer of the vessels. Calomel is endowed, therefore, with all the attributes of a curative agent, provided it is used with adequate energy.*

Referring to the great mortality of cholera infantum as given by most competent authorities, Rotch, Holt and Jacobi, viz., two-thirds of all cases treated, W. H. Wallace[60] states that, inspired by my views as given in the first volume[61] in respect to this disease, he had resorted to active stimulation which included calomel, $\frac{1}{4}$ grain (0.016 gm.), every half-hour until signs of bile appeared in the stools, and had been able to save his two last cases. Stengel[62] gives $\frac{1}{8}$ grain (0.008 gm.) every four hours, but I do not consider this dose adequate. Taylor and Wells[63] recommend $\frac{1}{40}$ to $\frac{1}{30}$ grain (0.0016 to 0.002 gm.) every fifteen minutes until two or three grains (0.13 or 0.2 gm.) have been administered.

Contrary to what is taught in text-books, the so-called "hyperpyrexia" should *not* be combated.* The high temperature being central only and due to the accumulation of blood in the deeper vessels, especially the splanchnic area, every effort should be made to restore the equilibrium of the circulation by measures which promote cutaneous hyperæmia:* by rubbing with warm flannel; warm baths—beginning with 98.6° F. (37° C.), the normal temperature, and raising it gradually to 105° F.

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* *Author's conclusion.*

[60] Wallace: Va. Med. Semi-monthly, July 22, 1904.

[61] *Cf.* vol. i, pp. 47 and 773 in the first two editions.

[62] Stengel: No. Carolina Med. Jour., Apr. 20, 1899.

[63] Taylor and Wells: "Dis. of Children," p. 205, 1899.

(41.8° C.); hot-water bottles, etc., the very measures indicated in the corresponding stage of Asiatic cholera.

Although various authors compare the frigidity of the surface in cholera infantum to the algid stage of cholera, they recommend cold baths in the former and hot bottles in the latter. Cold baths might prove of service by promoting the formation of waste-products and, through these, stimulation of the adrenal center; but the paucity of blood in the skin to which the frigidity is due defeats this action and annuls the value of the remedy. Roeder[64] recommends a warm mustard bath, followed by rubbing and placing of the child in a warm bed, "every effort being made to sustain the body warmth."

As soon as the intestines are satisfactorily cleared by the calomel, flushing of the colon is indicated, using lukewarm *normal saline solution,* one pint (500 gm.). Simultaneously a small quantity of the solution, 2½ drachms (10 gm.), should be injected hypodermically—repeatedly in severe cases. The sensitiveness of the skin being reduced, owing to the deficiency of blood, the child hardly feels the prick of the needle. When dehydration by copious and repeated serous stools is present, large quantities, 6 to 8 ounces (180 to 250 gm.), should be injected subcutaneously.

As stated by Stengel,[65] flushing of the colon and tepid baths will cause the symptoms to abate. Epstein[66] observed prompt improvement and rapid recovery in apparently hopeless cases by means of small doses of saline solution injected subcutaneously. Loin[67] injected 14 drachms (56 gm.) night and morning in infants from three weeks to six months old, and found it effective after every other measure had failed. Many other reports of this kind are available. Blackader[68] states that 8 ounces (236 gm.) or more, injected at once into the subcutaneous tissues of the thigh, abdomen or buttock, repeated twice daily if necessary, usually causes marked improvement of all symptoms.

When the case is seen after the serous stools have started, agents which stimulate the sympathetic center are necessary in addition to the foregoing measures, to reduce the caliber of the arterioles which this system governs.* *Morphine* is an active agent of this kind (especially after the osmotic properties of the blood have been restored by the use of saline solution in small or large doses) when given hypodermically in $^1/_{100}$-grain (0.00065 gm.) doses for a one-year-old child. Or, one or more drops of the *tincture of opium* may be given in an enema, according to age. *Atropine* is another valuable agent of this kind, and is, on the whole, safer for infants, $^1/_{500}$ grain to $^1/_{250}$ grain (0.00013 gm. to 0.00026 gm.), according to age, being well borne subcutaneously. By augmenting the propelling power of the arterioles, it drives blood into the peripheral capillaries, thus counteracting the hypothermia.[*]

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* *Author's conclusion.*

[64] Roeder: Die Therapie der Gegenwart, June, 1904.

[65] Stengel: *Loc. cit.*

[66] Epstein: Cited by H. F. Thompson: Med. News, Apr. 25, 1903.

[67] Loin: Semaine méd.; Brit. Med. Jour., Nov. 20, 1897.

[68] Blackader: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. ii, p. 228, 1898.

As emphasized by Potter,[69] opium should never be given when the discharges are green, slimy or offensive. Jacobi[70] recommends the warm enemata containing some alcohol and one or more drops of laudanum. The use of atropine has been recommended by many reliable observers. Sterrett[71] states that under the influence of $^1/_{250}$ grain (0.00026 gm.) in water, one such granule being given for each year of the child's age, every fifteen or thirty minutes, "the vomiting usually ceases, the skin becomes warm and the circulation equalized." Carefully dosed granules, such as those of the Abbott Company, should be used, to avoid untoward effects.

INFANTILE DIARRHŒA.

SYNONYMS.—*Summer Diarrhœa; Acute Gastro-enteritis; Dyspeptic Diarrhœa.*

Definition.—Infantile diarrhœa—a disease caused in most instances by the substitution of artificial foods for breast milk, which, owing to the auto-antitoxin it contains, protects the nursling against infection—is due to excessive irritation of the intestinal mucosa by toxic substances, especially the toxins of bacteria ingested with cow's milk.[**]

Symptoms.—These vary according to the location of the inflammatory process. If the small intestine is involved alone, the symptoms of *acute dyspeptic enteritis* prevail. The first of these, in the majority of cases, are restlessness, peevishness, and a slight fever, attended perhaps with slight colic, looseness of the bowels and nausea. These phenomena gradually become more severe until vomiting and purging occur. The stools, which at first may have contained undigested food detritus, are now and then offensive, green or greenish-yellow or brown. The temperature rises, reaching sometimes 104° F. (40° C.), the pulse being rapid and feeble. As the stools become more frequent, emaciation progresses rapidly, the child's aspect changing greatly within a few days. In some cases the onset is more sudden, all the symptoms enumerated coming on in rapid succession from the first, including the high fever, but excepting the purging. As the latter appears the temperature may recede one or more degrees. In this class of cases nervous phenomena are apt to prevail, *i.e.*, marked restlessness, delirium and even convulsions. Prostration increases as the disease progresses until slight cyanosis, coldness of the extremities and rapid diminution of the child's suffering indicate impending death.

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[*] *Author's conclusion.*

[**] *Author's definition.*

[69] Potter: Annals of Gynec. and Ped., Apr., 1898.

[70] Jacobi: Pediatrics, July 1, 1896.

[71] Sterrett: Annals of Gynec. and Ped., Aug., 1904.

When the inflammatory process is located chiefly in the ileum and colon, constituting *acute entero-colitis*, the earliest symptoms are, as a rule, similar to those of the preceding condition, but they come on abruptly and are supplemented by others which point directly to the large intestine as their source. Thus, while early vomiting is marked when the small intestine is alone involved, it is much less severe when the lesions are mainly located in the colon; the abdomen is apt to be tense, swollen and tender along the course of the colon. Various symptoms that recall dysentery also appear, *i.e.*, considerable mucus and more or less blood in the stools, straining, pain and sometimes intestinal prolapse during defecation. The stools are not copious as in dyspeptic enteritis, but small, and, as a rule, quite green, though sometimes brown. In rare cases shreds of pseudo-membrane are also passed. The prostration and nervous phenomena observed in dyspeptic enteritis may also occur, but ulceration of Peyer's patches and other intestinal glands causes these cases often to assume a typhoid type. Wasting progresses rapidly and the infant is almost reduced to a skeleton when, as usually happens, the case lasts five or six weeks.

The chances of recovery depend greatly upon the environment of the infant and its condition. Among the well-to-do the prognosis is far more favorable than among the poor, owing to the unsanitary surroundings of the latter, and also to the fact that their children are often puny and ill-fed.

Pathogenesis and Pathology.—The one great cause of infantile diarrhœa, of the millions of lives it has cost, and of the thousands of infants it is killing each year, is *the substitution of artificial foods of any kind,* including cow's milk supposedly adjusted to the physiological needs of the human organism, *for Nature's own food, the mother's milk, or failing it, breast-milk.*

Telling in this connection are the following lines by no less an authority than Jacobi:[72] "Amongst those who believe in the omnipotence of chemical formulæ, there prevails the opinion that a baby deprived of mother's milk may just as readily be brought up on cow's milk; that is easily disproved. In Berlin they found amongst the cows'-milk-fed babies under a year, the mortality was six times as great as amongst breast-fed infants. Our own great cities gave us similar, or slightly smaller, proportions, until the excessive mortality of the very young was somewhat reduced by the care bestowed on the milk introduced into both our palaces and tenements. Milk was examined for bacteria, cleanliness and chemical reaction. It was sterilized, pasteurized, modified, cooled, but no cow's milk was ever under the laws of Nature changed into human milk, and with better milk than the city of New York ever had, its infant mortality was greater this summer [1904] than it has been in many years. That hundreds of thousands of the newly-born and small infants perish every year on account of the absence of their natural food, is a fact which is known and which should not exist."

The statistics of the question point overwhelmingly in the same direction. Emmett Holt found that of 1943 fatal cases of digestive disorders, only 3 per cent. had been breast-fed. In a series of 718 fatal cases of infantile diarrhœa in Liverpool, studied by Jones,[73] the proportion of breast-fed infants was nearly as low, *i.e.*, 4.2 per cent. He states that in Munich the general mortality among breast-fed infants is 15 per cent., while in artificially-fed infants it is 85 per cent. J. Lewis Smith says that at Lyons, where foundlings (a class of infants, the parents of which are often alcoholics, syphilitics, etc.) are wet-nursed, the mortality is 337 per thousand, whereas at Aix, also a provincial city, where they are fed artificially, it is 80 per cent. In New York it reached nearly 100 per cent. until wet-nurses were provided. Winters[74] states that "during the siege of Paris (1870-71), while the general mortality was doubled, that of infants was lowered 40 per cent. owing to mothers being driven to suckle their infants!" "In my own experience," writes Holt, "fatal cases of diarrhœal diseases in nursing infants are extremely rare."

The enormous mortality in artificially-fed infants is due to the fact that none of the artificial foods, including cow's milk, even when obtained under the most favorable conditions and accurately adjusted as to proteids, carbohydrates, inorganic salts, etc., to the composition of human milk, supply the infant with bactericidal and antitoxic constituents that breast-milk contains, *i.e.*, the lacteal auto-antitoxin.* This immunizing substance serves not only to prevent infection of the infant's alimentary canal, but it penetrates into its blood to afford protection against infections of all kinds.*

Ehrlich[75] showed that milk was rich in antitoxin, though less so than blood, as he subsequently found with Wassermann.[76] As stated by

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* *Author's conclusion.*

[72] Jacobi: Amer. Medicine, Nov. 5, 1904.

[73] Jones: Brit. Med. Jour., Sept. 29, 1894.

[74] Winters: Med. Record, Mar. 7, 1903.

[75] Ehrlich: Zeit. f. Hyg., Bd. xii, S. 183, 1892.

[76] Wassermann: *Ibid.*, Bd. xviii, S. 243, 1894.

Metchnikoff, "the chemical composition of antitoxin is unknown." That the milk's antitoxin is similar to that in the blood, *i.e.* of auto-antitoxin, is demonstrated by the presence of the three constituents of the latter. The presence of *adrenoxidase* is shown by the fact that Babcock and Russell,[77] Dupouy,[78] Raudnitz,[79] Arnold,[80] Neumann Wender[81] and others have all found an oxidase in milk which colored guaiac blue. The last-named investigator also found that milk contained a proteolytic enzyme which he refers to as *trypsin* or galactase. Spolverini[82] found both trypsin and pepsin, and his observation was confirmed by Nobécourt and Merklen[83] and others. We have seen that the *nucleo-proteid* was also present as a constituent of fibrinogen. There can be no doubt as to the immunizing agencies being the same as in the blood. Van de Velde and Landstheer[84] found that all the milk ferments were also present in the blood.

The bacteriolytic property of the blood, according to the Buchner school, is due to alexins which, as I have shown in the first volume, are similar in composition to antitoxin. E. Moro[85] found that the serum of breast-fed infants not only contained more alexins than artificially-fed ones, but that the proportion corresponded with that of the alexins in the blood of the maternal placenta. This indicates that it is the function of the mother's milk to supply the infant's blood with antitoxin, precisely as her blood did her fœtus in utero. This was emphasized by the investigations of Halban and Landsteiner,[86] which showed that the maternal blood was, as compared to that of the fœtus, more potent as a bacteriolytic and antitoxic agent and as an immunizing serum; and moreover, that it inhibited more actively fermentative processes. Metchnikoff[87] states that the passage of the antitoxin ingested with milk into the suckling's blood, has been confirmed by a large number of observations. Welch, in his Harvey Lecture, also says: "It is an important function of the mother to transfer to the suckling through her milk immunizing bodies, and the infant's stomach has the capacity, which is afterward lost, of absorbing these substances in an active state. The relative richness of the suckling's blood in protective anti-bodies, as contrasted with the artificially-fed infant, explains the greater freedom of the former from infectious diseases."

Although cow's milk is likewise rich in auto-antitoxin, the latter begins to lose its activity soon after milking, because its nucleo-proteid combines with the adrenoxidase, thus depriving the immunizing compound of its two activating agents.* The fluid portion of the milk thus becomes reduced to the condition of blood-serum, an excellent culture medium for bacteria. Hence the fact that in a few hours, especially during warm weather, milk is often found to contain enormous quantities of bacteria, benign and pathogenic.[*] Pasteurization destroys the majority of virulent bacteria, it is true, but it also destroys the bacteriolytic trypsin; boiling is still more efficacious as a bactericidal agent, but it destroys both the trypsin and the adrenoxidase, thus annulling the immunizing properties of the milk.[*] Milk sterilized by either method, though seemingly capable of nourishing the infant, fails, therefore, to supply its blood with the antitoxin required to protect it adequately, and it is vulnerable to infection both in the respiratory tract and in the alimentary canal.[*]

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* *Author's conclusion.*

[77] Babcock and Russell: Annual Report of Agric. Sta., Univ. of Wisc., 1897.

[78] Dupouy: Thèse de Bordeaux, 1897.

[79] Raudnitz: Zentralbl. f. Physiol., Bd. xii, S. 790, 1898.

[80] Arnold: Arch. f. Pharm., Nu. 41, 1881.

[81] Neumann Wender: Œsters. Chem. Zeit., 1902.

[82] Spolverini: Atti d. iv. Congr. Ital. de Ped., 1901.

[83] Nobécourt and Merklen: La presse méd., Dec. 24, 1902.

[84] Van de Velde and Landstheer: Arch. de méd. des enfants, vol. vi, p. 408, 1903.

[85] E. Moro: Jahrb. f. Kinderheilk., Apr., 1902.

[86] Halban and Landsteiner: Amer. Jour. Med. Sci., May, 1903.

[87] Metchnikoff: *Of.* vol. i, p. 371.

Trypsin was found in cow's milk by Spolverini,[58] Nobécourt and Merklen[59] and others. Gillet[60] found cow's milk rich in oxidase (adrenoxidase), thus confirming the observations of other investigators. Indeed, the literature of the subject shows that young mammals are but prototypes of the infant in the protection afforded by the maternal milk. While Freudenreich[61] and others found, for instance, that cow's milk when fresh destroyed cholera, typhoid and other pathogenic bacteria, Metchnikoff, referring to the investigations of Ehrlich and Wassermann,[62] states that "earlier researches had shown that it was only when mice were very young that they could assimilate antitoxins from the alimentary canal, while adult mice acquired no immunity, the blood showing no increase of antitoxic activity." This clearly points to the need of antitoxin in the blood of young mice to increase its antitoxic activity.

Indeed, in the light of my views, it is probable that the ferments in maternal milk do more than protect the offspring against infection, *i.e.*, that they *actually take part in its cellular metabolism*, *its very vital process*. Thus, while Ehrlich in 1900 laid stress on the fact that human milk contained ferments which made it superior to all methods of artificial feeding, Moro[63] showed by careful experiments on infants that while they gained in weight constantly upon normal breast milk, when the latter was sterilized by heat, thus destroying the ferments, the increase in weight was almost imperceptible. The failure of Lunin's chemically perfect artificial milk—in which, however, the ferments were not taken into account—thus becomes self-evident. Referring to the fact that in Lunin's method of preparing this milk the unorganized ferments were destroyed, L'espérance[64] remarks, quite in keeping with the estimates of Jacobi: "This fact explains why sterilized milk and other sterilized foods have not fulfilled the general expectations of the scientific world."

Given now an infant fed on perfectly "sterilized, pasteurized, modified, cooled cow's milk," what have we at best? An organism vulnerable to infection not only by way of the *alimentary canal*, but *also by way of the lungs*. Hence the appalling mortality among infants not only from intestinal disorders, but also from pneumonia, bronchitis and other pulmonary diseases. Suggestive in this connection is the fact that, in a series of 237 cases reported by various observers and summarized by Holt,[illegible] and in which the bacillus dysenteriæ of Shiga was found, 26 were breast-fed—a condition which, as he says, practically excludes the possibility of infection through milk. The only other channel is the respiratory tract, the intestinal irritation being caused by the elimination of the bacillus through the intestinal mucosa.

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[*] *Author's conclusion.*
[58] Spolverini: *Loc. cit.*
[59] Nobécourt and Merklen: *Loc. cit.*
[60] Gillet: Jour. de physiol. et de pathol. gén., vol. iv, p. 439, 1902.
[61] Freudenreich: Bacter. World, Dec., 1891; Jan., 1892.
[62] Ehrlich and Wassermann: *Loc. cit.*
[63] Moro: Jahrb. f. Kinderheilk., Oct., 1902.
[64] L'espérance: Med. Record, Mar. 19, 1904.

Under these conditions the daily and continuous use of contaminated milk is not required to infect the infant, a *single day's milk* or even a *single feeding of milk* containing a few pathogenic bacteria suffices to do so, since its secretions, its blood and its lymph are unable to prevent their proliferation.* A single relaxation of vigilance on the part of the infant's attendant involving secondary contamination of the milk after sterilization, an error in reading the thermometer during Pasteurization, careless cleansing of the vessels or bottles, etc., may thus entail the pathogenic importance of an inoculation through the skin—where a minute quantity of infectious material may provoke general infection.* . This is rendered possible by the fact that even milk drawn under the strictest antiseptic precautions contains over 300 bacteria per cubic centimeter; that ordinary fresh milk contains from 2000 to 40,000 bacteria in the same volume; and finally that the proportion of bacteria in the milk delivered in cities, especially during warm weather, ranges from 40,000 to 2,000,000 bacteria per cubic centimeter.

The proportions mentioned were obtained mainly from those published by Conn, in the bulletins of the Michigan State Agricultural College Experiment Station. The larger figures given may seem large, but they are probably below the average. Hamill,[illegible] for instance, states that "the number of bacteria sometimes found in ordinary market milks is almost incredible. As many as 100,000,000 per cubic centimeter have been found in the milk of Washington, D. C., and as many as 600,000,000 per cubic centimeter have been found in some milks in the city of New York. Of course," adds the author, "these figures are unusual, but a count of from 1,000,000 to 2,000,000 per cubic centimeter is not at all uncommon."

Among the pathogenic microörganisms that have been found in milk are streptococci, staphylococci, the bacilli coli and lactis aerogenes, and those which produce typhoid fever, diphtheria, glanders and tuberculosis. No special organism can be said to be the specific cause of infantile diarrhœa, but those most frequently found in the stools are the streptococcus, which occurs in the stomach, small and large intestine; the proteus vulgaris, found in severe cases, with putrid stools; the staphylococcus pyogenes; the bacillus pyocyaneus; the bacillus mesentericus; the bacillus enteridis, and finally a microörganism which has attracted considerable attention of late, the bacillus dysenteriæ of Shiga.

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* *Author's conclusion.*

[illegible] Holt: Rockefeller Inst. for Med. Research, vol. ii, p. 185, 1904.

[illegible] Hamill: Proceed. Phila. Co. Med. Soc., vol. xxiv, p. 124, 1903.

The presence of Shiga's dysentery bacillus in the stools of cases of summer diarrhœa, was pointed out by Celli and Valenti,[97] and confirmed by Duval and Bassett.[98] Flexner,[99] summarizing the results of observations in 412 cases studied bacteriologically by various investigators in four large cities, states that of this number 63.2 per cent. of all cases examined gave positive results. Holt[100] studied the clinical reports of 237 cases, and found the dysentery associated with every sort of intestinal disturbance accompanied by diarrhœa, with the notable exception of cholera infantum.

The lesions in the alimentary canal vary with the duration of the case. There may be slight gastritis with punctiform hæmorrhage. The upper portion of the intestine is rarely affected, the ileum, the ileo-cæcal valve and the colon bear the brunt of the morbid process. This may vary from hyperæmia to marked congestion, followed by ulceration of the enlarged follicles and Peyer's patches—the source of the typhoid symptoms witnessed. Bacilli are found both in the mucosa and submucosa and occasionally deeper. The two layers are sometimes involved in the necrotic process and become detached and voided in the stools as pseudo-membrane—a rare occurrence, as previously stated.

Treatment.—When infantile diarrhœa has developed, owing to any one of the morbid factors enumerated, the cardinal indication is to destroy the pathogenic elements both in the alimentary canal and in the blood. *Castor oil* has received the sanction of considerable experience, but it should be considered only as an eliminant. It starts the intestinal antitoxic process by increasing reflexly the secretory activity of the intestinal mucosa and a great step is made toward protecting the infant.* But this is inadequate to protect it properly.* Its adrenal system should be stimulated to unusual activity in order to increase the proportion of auto-antitoxin in its blood and intestinal juice.* *Calomel* is decidedly the best agent in this connection and should be begun as soon as the castor oil has produced its effect, 1/20 grain (0.003 gm.) every half hour until 1 grain (0.065 gm.) has been given. If the stools have not resumed their normal color, it should be continued, avoiding, however, salivation, which indicates, as I have shown, that the proteolytic—and therefore bacteriolytic and antitoxic—properties of the blood have become excessive.* The *biniodide of mercury* is quite as effective.*

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* *Author's conclusion.*

[97] Celli and Valenti: Centralbl. f. Bakt., Bd. xxv, S. 481, 1899.

[98] Duval and Bassett: Amer. Medicine, Sept. 13, 1902.

[99] Flexner: Rockefeller Inst. for Med. Research, vol. ii, p. 121, 1904.

[100] Holt: *Loc. cit.*

It is customary to combine the calomel with supposed antiseptics, such as resorcin, benzol-naphthol, etc., but they do more harm than good. It is a fallacy to believe that they act in the intestinal canal as they do in the laboratory. The alimentary canal being laden with adrenoxidase, these various drugs are broken up and their action is entirely modified.

I do not deem it necessary to submit evidence to the effect that castor oil and calomel are valuable in infantile diarrhœa. Reflecting only the prevailing knowledge as to their action, Blackader[121] writes: "For the evacuation of the intestinal tract two drugs especially commend themselves on account of their promptness and the very slight amount of irritation which they induce. These are castor oil and calomel." As to the biniodide of mercury, Luff[122] reported 80 cases, 72 of which were cured in two days as to the diarrhœa *per se*. He gave it in 1/8-grain (0.0082 gm.) doses in a solution of potassium iodide. Illingworth has also reported excellent results.

To remove the exogenous pathogenic factor goes without saying. If the infant is hand-fed, the best curative food is the milk of a wet-nurse, which supplies its alimentary canal and its blood with the antitoxin it requires.* *Diphtheria antitoxin* suggests itself as an effective agent in this connection.*

The value of the homologue of maternal milk, that of a wet-nurse, under these conditions, is self-evident. The change for the better is almost magical. In one of my cases twenty-four hours of wet-nurse converted a very ill infant to one in normal health—aside from the temporary emaciation and weakness. I saved my only son by this measure after all others, carried out by a friend and colleague, had failed. I cannot find evidence to the effect that diphtheria antitoxin has been tried in such cases; that it must be valuable—in the light of my views at least—is apparent.

The loss of considerable serum in choleraic cases depletes the child's blood both of fluids and alkaline salts, and the osmotic and antitoxic properties of the body fluids and the migration of phagocytes to bacteria-laden areas are thus greatly compromised.* This should be counteracted by large *enema* of *saline solution* at not less than 102° F. (38.9° C.), daily, during the period of serous discharge and once after its cessation. If the enema is at once voided with the stools, the solution should be given *subcutaneously,* 8 or 10 ounces (236 to 295 gm.) being injected very slowly.

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* Author's conclusion.

[121] Blackader: Sajous's "Analyt. Cyclo. of Pract. Med.," vol. iv, p. 18, 1899.

[122] Luff: Brit. Med. Jour., Nov. 18, 1893.

Many clinicians wait until the stage of collapse before using the saline solution; this is supported by no sound reason whatever. It would be as wise to allow a man to starve until death is near before giving him food.

If after the stools are no longer foul, the serous flux persists notwithstanding all the foregoing measures, small doses of *morphine* are necessary to provoke contraction of the intestinal arterioles, the excessive dilation of which underlies the flow.

To obtain this result astringents are usually employed, but these agents arrest function by causing constriction of the capillary walls. The preparations of opium, on the other hand, influence precisely the torpid center and the arterioles it governs, namely, the sympathetic center.

During the first few hours of treatment, the diet should be limited to barley water; as soon as improvement occurs, however, an increase of food is required.* This may be met by boiling a very fresh egg until its yolk is so hard that it can readily be reduced to a flour-like powder.* This powder added to the barley water or to equal parts of barley water and boiled milk, or to any other liquid food that may be adaptable, increases greatly its value as a nutrient, and supplies the infant with all the constituents its organism requires for a prompt convalescence.* A change of air, especially if the infant can be taken to the seashore, hastens convalescence very greatly.

The convalescence is often protracted, owing to the fact that the food administered does not contain enough phosphorus to build up the myelin lost during the illness, and the entire nervous system is adynamic and stays so. As stated by Shoemaker,[108] yelk of egg (vitellus) "is highly nourishing, and, as it contains phosphorus, it is especially restorative to the nervous system."

ACUTE ENTERITIS.

SYNONYMS.—*Acute Diarrhœa; Simple Acute Catarrhal Enteritis; Acute Ileo-colitis; Acute Intestinal Catarrh.*

Definition.—Acute enteritis, a disorder characterized by diarrhœa, is due to a reflex reaction of the intestinal mucosa which has for its purpose to antagonize the harmful effects upon it of noxious substances contained in the ingesta, or in the substances which the mucosa itself eliminates.**

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* *Author's conclusion.*

[108] Shoemaker: "Materia Med. and Therap.," p. 918, 1908.

Symptoms.—The most prominent symptom of this condition is diarrhœa. The stools, which are at first fæcal, become yellowish or colorless, and finally watery and frothy, and occur with increasing frequency. Though offensive at first, they sometimes lose all odor. When examined microscopically, they are found to contain leucocytes, erythrocytes, broken-down columnar epithelium, various non-pathogenic bacteria, and the bacillus coli commune, food detritus and other substances which vary according to the segments of intestines involved. The salient symptoms are colicky pain, borborygmus, flatulence, some abdominal tenderness with gurgling on pressure, oliguria due to the loss of fluids, anorexia and sometimes slight fever.

Unless the diarrhœa be the forerunner of some graver condition, as is often the case during cholera epidemics, or the initial stage of chronic enteritis, the symptoms disappear gradually after the second or third day.

Pathogenesis and Pathology.—Enteritis is caused by any substance capable of irritating the intestinal mucous membrane. It represents, at first, a (vagal*) reflex increase of functional activity of the intestinal glandular and muscular elements by the irritant, having for its purpose the protection of the mucosa and the body at large. Intestinal juice containing auto-antitoxin and mucus (the latter serving to protect mechanically the cellular elements of the mucosa), the former is produced in abundance, to disintegrate by cleavage the irritating substance and insure its elimination.*

The irritation of the intestines may be *exogenous,* i.e.*, caused by ingested materials, unripe fruit, fermented foods, an excess of food-stuffs, or foods containing a small quantity of leucomains (those containing a large quantity of leucomains, stale cream-puffs, ice-cream, cheese, etc., give rise to cholera morbus, in which the central nervous system is involved*), unripe fruit, impure drinking water, etc.; or *endogenous, i.e.*, produced by irritants originating in the body. Toxic wastes, formed when the body is exposed to cold and damp or when the surface of the abdomen is suddenly chilled,* frequently cause enteritis. The temperature of the cellular trypsin being lowered, the cutaneous catabolic processes are inhibited, and as imperfectly broken-down wastes are poisonous, they irritate the intestinal canal while being eliminated through it.* The toxic substances of bacterial origin, of detritus, acids, etc., formed during typhoid fever and other febrile diseases, cancer, Bright's disease, tuberculosis, etc., produce enteritis by the same morbid action on the intestinal canal.*

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* *Author's conclusion.*
** *Author's definition.*

Treatment.—In mild cases due to ingested irritants, a restricted diet, particularly if anorexia be present, usually suffices to insure early recovery, since the intestinal overactivity is thus to a great extent reserved for the disintegration and elimination of the offending substances. When a case presents any degree of severity, however, the auto-protective process should be aided by administering a purgative. *Magnesium citrate*, the entire bottle being taken in two doses, usually suffices for the purpose and materially reduces the duration of the diarrhœa. *Calomel*, in $^1/_4$ grain (0.016 gm.) doses for adults, every half hour until eight doses have been taken, is also very effective. By actively stimulating the adrenal center, it increases the activity of the pancreas, and therefore the antitoxic activity of the intestinal juice, while acting as a purgative.* Smaller doses are also efficacious, though *castor oil* is preferred by many clinicians.

After elimination of the irritant substances measures may be taken to arrest the diarrhœa. This may be done by giving small doses of *opium*, $^1/_2$ grain (0.03 gm.), to constrict the arterioles.* If there is any suspicion that the cause is not completely removed, *belladonna* is preferable, since it not only reduces the caliber of the arterioles, but enhances their propulsive activity, thus increasing the volume of arterial blood which circulates in the capillaries of the intestinal mucosa.* A granule of $^1/_{100}$ grain (0.00065 gm.) three times daily, then twice daily, suffices. If there is any degree of general adynamia, *thyroid gland* 1 grain (0.06 gm.) after each meal not only counteracts this condition, but while doing so, hastens resolution of any intestinal lesion that may be present.*

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* *Author's conclusion.*

CHRONIC ENTERITIS.

Synonyms.—*Chronic Diarrhœa; Chronic Entero-colitis; Ulcerative Colitis; Mucous Colitis; Tropical Diarrhœa.*

Definition.—Chronic enteritis, a disorder characterized by persistent diarrhœa, is due to irritation of the intestinal mucous membrane by imperfectly digested food-stuffs, or by protozoa. The diarrhœa is the expression of a protective process having for its purpose the destruction and removal of the pathogenic substance or parasite.*

Symptoms.—When it does not occur as a result of acute enteritis, the chronic form comes on insidiously, the first indication being looseness of the bowels, occurring coincidently in most cases with gastric malaise. The movements gradually increase, however, both as to number daily, though they seldom exceed five, and as to quantity, and are apt to occur after rising in the morning or immediately after a meal. The first daily stool is usually fæcal, but the succeeding ones gradually become more liquid until they are watery, though yellowish-brown in most instances. The typical stools are clay-colored and usually contain considerable mucus, the terminal stool of the daily series being often entirely mucoid, sometimes streaked, in advanced cases, with blood. They are often described as "sago-like," the mucus being broken up into granules. At times they are bile-stained and brownish-yellow.

Microscopically, the stools are usually found to contain fragments of food, carbohydrates as well as proteids, in various stages of digestion, starch granules, fat globules, cholesterin plates, triple phosphate crystals, etc. Occasionally, especially in women, the mucus is discharged in the form of casts of various segments of the colon. Examination of the rectum in advanced cases reveals marked local congestion and areas of ulceration, the whole being coated with mucus. In the proximity of the anus the mucous membrane is usually found thickened and excoriated, owing to constant contact with abnormal excrementitious products. The sphincter being extremely irritable, tenesmus is often complained of—a cause in some cases of constipation, followed sooner or later by a copious discharge. Pain is sometimes complained of, but it amounts seldom to more than slight colic. Tenesmus and flatulence are prominent features. Another salient symptom in some cases is a voracious appetite, though the patient is usually asthenic, even his temperature being sometimes below normal.

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* *Author's definition.*

In tropical countries especially, including the Philippines, various protozoa, the balantidium coli in particular, may cause obstinate diarrhœa. The stools are generally bloody and contain the organism, while the blood of the general circulation is found to contain an unusual number of eosinophile leucocytes.

Pathogenesis and Pathology.—Chronic catarrhal enteritis may be due to the presence in the intestinal canal of foodstuffs (both proteids and carbohydrates) that have been imperfectly hydrolized to peptones and proteoses in the stomach, and which therefore act as irritants. Any disease of the stomach in which the digestive process is sufficiently impaired may thus give rise to this form of enteritis, also termed "lienteric diarrhœa." The imperfectly digested foods, owing to their irritating nature, stimulate reflexly the intestine to increased activity,* secretory and peristaltic, to such a degree that in the majority of cases the bowels are evacuated immediately after a meal, the stools containing considerable undigested material.

In another class of cases, the digestive process is inadequate in the intestine as well as in the stomach, the secretion of pepsin and trypsin being markedly reduced, and the gastric motricity and intestinal peristalsis likewise. Dilation of the stomach and enteroptosis are sometimes observed in these cases, owing to muscular relaxation, and the diarrhœa often tends to alternate with periods of constipation. This form is primarily due to conditions which markedly debilitate the adrenal system.* These include exhausting diseases such as tuberculosis, malaria, anæmia, syphilis, and influenza; conditions which overtax the muscular system, such as long marches with heavy accoutrements and other causes of fatigue; insufficient or indigestible food; dirt-eating, etc. The excessive heat of tropical countries also predisposes to chronic catarrhal enteritis, *i.e.*, tropical diarrhœa, the debilitating influence being the loss of reflex excitation of the central nervous system which cold insures by exciting the cutaneous sensory organs.*

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* *Author's conclusion.*

Various protozoa may provoke persistent chronic diarrhœa by causing ulcerative enteritis. Prominent among these is the balantidium coli of Malmsten (1846) which penetrates the mucosa and submucosa, and by multiplying rapidly, brings about organic changes that may cause death in a few months. It is ingested by drinking water infected with the balantidium of pigs, in which it is common. The amœba coli, one of the causes of tropical dysentery, and the strongyloides intestinalis of Havay (1876) may also cause obstinate diarrhœa by giving rise to ulcerative enteritis.

That chronic diarrhœa may be of dyspeptic origin is now generally recognised, thanks to the labors of Ewald, Nothnagel, Rosenbach, Penzoldt, Einhorn and others. The same may be said of the asthenic form. As stated by Allen A. Jones,[154] "In the gastric affection named by Einhorn 'Achylia Gastrica,' there exists a suspension of the secretions of the stomach, in some cases as the result of atrophy of the gastric glandules, in others as the result of a nervous disturbance of secretion. It is probable that all cases of this affection do not arise from glandular atrophy. For some years Stockton has maintained that the disorder often begins, and may continue, as a neurosis, and he has found a special form of ocular refractive error associated with it. In writing upon 'Gastric Anacidity' some years ago," adds the author, "I also emphasized the suggestion that some cases perhaps commence as a neurosis and may go on to subsequent organic disease and atrophic changes." He considers as results of such a condition, a precipitate expulsion of food with irritation or overwork of the intestine, caused by the toxic substances developed and more or less severe inflammation of the intestine. That the adrenal center is primarily affected is shown by the nature of the diseases which give rise to it, *i.e.*, "chronic exhausting diseases," as Tyson[155] characterizes them.

That the balantidium coli may also produce lesions other than those found in the colon, may be illustrated by a case reported by Strong and Musgrave,[156] in which the jejunum and ileum were both hyperæmic and contained considerable mucus.

Treatment.—The chronic catarrhal enteritis due solely to gastric disorders, requires, of course, appropriate measures calculated to remove the latter. Attention to the *diet* is also of paramount importance: cereals, fruit and vegetables leaving much waste, iced foods or beverages, fried or highly seasoned foods, or substances cooked in much fat, etc., should be avoided and replaced by easily digested articles. Over-eating and drinking is a prolific source of the disease in tropical countries. Alcohol is always contraindicated, since it deoxidizes the adrenoxidase of the gastric juice and lowers its digestive activity in proportion.*

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* *Author's conclusion.*

[154] Allen A. Jones: Jour. Amer. Med. Assoc., July 30, 1898.

[155] Tyson: *Loc. cit.*, p. 382.

[156] Strong and Musgrave: Bull. of Johns Hopkins Hosp., Feb., 1901.

Fresh water, without ice, should be used as a sole beverage. *Bismuth subnitrate,* in 15-grain doses (1 gm.), taken one hour before each meal, and washed down slowly with a half-tumblerful of water, is carried by the latter directly to the intestine, and markedly reduces the local congestion before the next meal enters the canal. Towards the end of each meal, 5 grains (0.3 gm.) of *pepsin* aid considerably the digestive process and avoid the formation of the intestinal irritants. If there is gastric atony, and the digestion be abnormally slow, a small pill composed of extract of *gentian,* $^1/_2$ grain (0.033 gm.), and extract of *nux vomica,* $^1/_4$ grain (0.016 gm.), taken twenty minutes before each meal in addition to the foregoing measures, is indicated. In mild cases, these remedies, a light diet, and rest —since a considerable portion of muscle-wastes are eliminated by way of the intestine and tend to aggravate the local lesions— soon prove beneficial and, if persisted in, curative. In severe cases, the reduced diet should be replaced by an all-milk diet, taking care that the patient be supplied daily, distributed throughout the three meals, the quantity of *sodium chloride* eliminated daily with the urine, *i.e.,* $^1/_2$ ounce (15.5 gms.).[*]

The milk treatment fails in many cases because the fact is overlooked that milk is very poor in sodium chloride. This salt is all the more essential in that it takes part in the formation of the gastric hydrochloric acid, which plays in the present disorder a cardinal rôle as will be shown presently.

The treatment of the neurasthenic form differs from the preceding in that the main indication is to raise the functional activity of the adrenal system to its normal level and thus increase the functional activity of the stomach and pancreas.[*] The treatment—dietetic and medicinal—indicated in the first form, is likewise of advantage here. After a week or so, however, when the acute irritability of the intestinal canal begins to disappear, as shown by a marked diminution of the number of stools and of the tenesmus and general discomfort, the pepsin should be omitted, and a capsule containing *strychnine sulphate,* $^1/_{40}$ grain (0.0016 gm.), and *thyroid gland,* 1 grain (0.06 gm.), given during each meal to increase the proportion of auto-antitoxin in the intestinal secretions.[*] The diet can then be increased gradually to the normal quantity, the patient being warned to avoid foods that produce bulky wastes, irritating condiments, and alcohol, and any kind of food which he has found by experience is digested with difficulty. Cases in which there is a history of syphilis yield promptly to treatment addressed to this condition. High enemata of normal *saline solution* at 104° F. (40° C.) hasten materially the curative process in all forms of chronic diarrhœa.

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[*] Author's conclusion.

When the general asthenia is not marked, regulation of the diet, the bismuth before meals and strychnine during the meal usually prove efficacious. The functional torpor of the pancreas may be counteracted and recovery greatly hastened, however, by administering *dilute hydrochloric acid,* 20 to 30 drops in water after meals. On reaching the duodenum the acid stimulates the pancreas and causes it to increase its production of trypsin. This enhances not only the efficiency of the intestinal digestion, but also the intracellular functions of the digestive leucocytes and, therefore, general nutrition.*

The treatment of chronic diarrhœa depends upon the identity of the parasite, as far as local treatment is concerned; thus, rectal injections of *quinine,* 1 in 1000 solution, kill the balantidium, but do not affect the amœba coli. A solution of 1 in 10,000 of *silver nitrate* used in the same manner is sometimes effectual in destroying the latter. *Calomel,* in small doses, has been recommended by several observers; it acts, as we have seen, by increasing the proportion of auto-antitoxin in the intestinal juice, owing to its powerful stimulating action on the adrenal system.*

We have seen that potassium iodide and mercury are most potent adrenal stimulants. In a case in a syphilitic subject reported by Lereboullet,[107] the diarrhœa, which had lasted eighteen months and had resisted all treatments, promptly yielded to anti-syphilitic measures. The same treatment is in reality effective irrespective of any syphilitic disease. Its action through the adrenal system is supplemented by a direct effect on the organisms. Quincke[108] states that calomel is toxic to all protozoa. Hydrochloric acid has been found very useful by Allen A. Jones,[109] Soupault,[110] Aaron[111] and others.

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* *Author's conclusion.*
[107] Lereboullet: La semaine méd., July 4, 1900.
[108] Quincke: Berl. klin. Woch., Bd. xxxvi, S. 1061, 1083, 1899.
[109] A. A. Jones: *Loc. cit.*
[110] Soupault: Le bull. méd., vol. xvi, p. 255, 1902.
[111] Aaron: Medical Age, Feb. 25, 1902.

TYPHOID FEVER.

SYNONYMS.—*Enteric Fever; Abdominal Typhus; Nervous Fever; Autumnal Fever.*

Definition.—Typhoid fever, a disease characterized by the penetration into the intestinal lymph follicles, and often into the fluids of the body at large, of the bacillus typhi or of the bacillus coli (when the latter has assumed virulence) and their toxins or endotoxins, is the expression of a reaction of the adrenal system, having for its purpose to rid the body of these pathogenic germs and their poisons.*

Symptoms.—The incubation period lasts generally two or three weeks, occasionally less. The symptoms appear gradually, beginning with a feeling of weariness, slight nausea, loss of appetite, sometimes diarrhœa. The tongue becomes coated, the expression dull. Pain is often present as headache, and in the back and legs; in the head and neck it is sometimes so severe and persistent as to resemble that of meningitis. The rise of temperature is usually gradual, sometimes sudden, to reach 102° F. (38.9° C.) or even 103° F. (39.5° C.) by the time the disease is well started. Chills of varying severity, followed by sweats, are not unusual. At the onset, delirium and bronchitis may also be seen, the latter especially in children. In the pneumonic and renal types of typhoid, the nature of the disease is likely to be marked for some days by evidences of pneumonia or acute nephritis; at the end of this period the diagnosis is warranted if fever is observed to continue.

The disease is generally considered to have begun when the patient is obliged to take to bed. From this time on it is found convenient to summarize the symptoms as they occur in successive weekly periods.

First Week.—The pains already mentioned persist. The intellect is generally blunted, but this is not an infallible sign. Wakefulness is sometimes met with, but there is usually no delirium in the first week. Fever continues, and the skin is hot and dry; a diffuse erythematous rash may appear. The daily temperature shows a slight rise from morning to evening; it also rises gradually throughout the week. The pulse shows greater frequency, less marked, however, than the temperature rise; it is easily compressed and often dicrotic.

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* Author's definition.

Near the end of this period, spots of a rose color appear on the skin, usually on the abdomen. They number usually not more than twenty or thirty, except in those cases where the distribution is widespread. Other symptoms include nausea, disinclination to take solid food, white furred tongue, diarrhœa (occasionally constipation) and slight cough. At the end of the week the spleen is found to be enlarged, but it is rarely the seat of pain. The urine is usually lessened.

Second Week.—The symptoms become more severe. There is rapid loss of strength. Dullness of countenance and apathy increase, until the face shows little or no expression; deafness is an additional factor. The headache slowly disappears, and is replaced by delirium of variable severity, more apt to be of a quiet, muttering character than otherwise. The rose-colored spots appear on the abdomen and chest in successive crops, each lasting three or four days, and leaving a slight discoloration of the skin. The temperature remains high and may rise above that attained in the first week; diurnal variations continue. The height which it reaches affords commonly, but not invariably, an indication of the severity of the case. The pulse-beat shows a rise in frequency, but usually does not exceed 100 until the latter part of the second week. The first sound of the heart is perceptibly lowered in volume, and congestion in the lungs may appear as an evidence of cardiac weakness. Moist and dry râles may be heard. The tongue again has a white, furry coat; later this disappears, leaving the tongue bare and red, with a tendency to become dry and cracked. The lips are similarly affected. Commonly the mouth contains mucus, which renders it sticky and hinders mastication, and provokes thirst, while the gums and tongue are apt to bleed. The stomach is less irritable than during the first week, but in general nausea and anorexia persist. The abdomen is now found to be tympanitic, owing to the accumulated gases resulting from fermentation and the inability of the weakened muscular layer to drive it out. Constipation may occur, but more commonly there are numerous diarrhœal evacuations, ochre-yellow in color, copious, liquid, with shreddy matter and offensive odor.

In these stools the bacillus of typhoid can be detected in the course of the second week. Death occasionally occurs toward the end of this period, owing to perforation of the intestine.

Third Week.—Muscular weakness and emaciation have become marked. Delirium is continued, depending in severity on the individual. In the severe type it may be replaced by coma vigil and subsultus tendinum. Staring eyes and flushed skin give the face a peculiar expression; the patient is no longer conscious. The rose-colored spots continue to appear. Repeated sweats occur at this stage, in a few cases earlier in the course of the disease. They are followed by eruption of small, temporary vesicles or sudamina. The temperature continues high, but with more considerable remissions, the morning and evening determinations differing sometimes by three or four degrees. The pulse is now found to be more frequent and small in volume. The cardiac first sound is markedly weakened. In bad cases breathing may be shallow and hastened.

Diarrhœa is continued and may be severe; large numbers of bacilli are present in the stools. Sometimes the stomach remains irritable, and the resulting insufficient nutrition causes the patient to become exhausted. Jaundice is occasionally seen; with it is often associated epistaxis of corresponding severity. In such cases the stools are dark colored and the urine contains albumin. Thrombosis of the veins is not uncommon and usually occurs in the legs. Dilation of the heart from degeneration and weakening of the musculature should be watched for; the first sound is decreased and the second pulmonic accentuated. The quantity of urine is now greater, and its toxicity remains high, particularly when treatment with cold baths has been used. Typhoid bacilli are found in the urine in twenty-five per cent. of all cases.

At this stage perforation and hæmorrhage are commonest. These are favored by the accumulation of gas in the bowel. Hæmorrhage occurs in about 5 per cent. of the cases and is fatal in one-third of this number. It may be gradual and slight in amount, or sudden and voluminous. The symptoms, which sometimes appear before hæmorrhage has occurred, include lowered temperature, cold skin, weak and frequent pulse. The likelihood of fatal result is indicated by the degree of prostration of the patient. In general, the loss of blood is followed by cessation of delirium and return of consciousness. Pain is present in some cases of hæmorrhage.

Perforation of the intestine is accompanied by a fall in temperature, also by a cold skin and increased pulse-rate, as in the case of hæmorrhage. There is sudden pain in the belly, in most cases; the abdomen is at first tense, but soon shows swelling from the escape of gas from the gut. The face has a pinched expression, and the rate of respiration is increased. Vomiting is not uncommon. The urine may be lessened in amount. Death almost invariably follows perforation, either at once from collapse, or in the course of a few days from peritonitis. Perforation and peritonitis sometimes follow hæmorrhage, but it may occur without perforation. Death can result from complicating inflammations in various portions of the body, commonly in the lungs. This may occur in cases otherwise apparently mild.

Fourth Week.—In this period the symptoms usually diminish in severity, and convalescence begins. Sweats are likely to persist. The temperature gradually falls and becomes intermittent, being normal in the morning and rising again in the evening. Additional elevations may be noted as the result of excitement, exertion, or mistakes in diet. The pulse-rate usually subsides to normal, but may remain high for some time. Evidence of continued cardiac weakness is sometimes seen in œdema of the lower extremities, and thrombosis of the veins is common in this stage. Boils and bed-sores may occur, and the hair has a marked tendency to fall out. Inflammation of the bones is not unusual in the young during convalescence.

In more serious cases of typhoid, the symptoms may continue through the fourth and fifth weeks. Sometimes the temperature may show irregular and rapid rises and falls of wide range. Emaciation and weakness are marked in these prolonged cases. The pulse becomes very weak, and the sphincter muscles lose their tonicity. Death may occur from perforation, exhaustion, or cardiac failure.

Pathogenesis and Pathology.—The bacilli of the typhoid group include the colon bacillus and, whether as a result of rapid multiplication of the latter or of the assumption by it of greater activity, it can assume the virulence of the typhoid bacillus irrespective of any infection, when the environment is suitable. In the intestinal canal, which contains constantly the bacillus coli communis, the condition which renders possible such an assumption of virulence by this germ is the presence in the intestinal juice of an insufficient proportion of auto-antitoxin.[*]

Typhoid fever may be caused, therefore, without infection of external origin when, either through hypoactivity of the adrenal system, or through excessive utilization of the blood's adrenoxidase (as during exhaustion and prolonged exertion or labor), the proportion of auto-antitoxin in the body at large is inadequate.[*] This accounts for the development of typhoid fever in the so-called "spontaneous origin" group: in troops, after long and exhausting marches, in the overworked and debilitated, etc., where there is no evidence of infection by typhoid bacilli of exogenous origin.[*]

In the great majority of cases, however, the disease is caused by typhoid bacilli ingested with food or beverages, especially water derived from a contaminated source. While debilitated individuals, *i.e.*, individuals in whom the adrenal system is hypoactive (and whose intestinal juice is therefore poor in auto-antitoxin) are more readily infected,[*] subjects in apparently normal health do not seem to be exempt.

The close kinship between the colon bacillus and the typhoid bacillus is now generally recognized. Ohlmacher[112] writes in this connection: "One of the most significant arguments for the close relationship of these bacterial groups seems to be afforded by the now generally adopted practice of 'rejuvenating' bacilli of the colon group secured from saprophytic surroundings, as from *water*, by growing them for several generations under the artificial laboratory environment before making physiologic differential tests." . . . "Many of the acquired characteristics make a suspiciously typhoid-like behavior in a so-called colon bacillus."

The development of typhoid fever among troops during hard campaigns involving much fatigue, is well known. Houston[113] states that "the efficiency of the army medical service, although high, has failed to prevent the British troops in South Africa from suffering from enteric fever to a deplorable extent." Constans of Montpellier[114] showed twelve years ago, that fatigue was a very important factor in the pathogenesis of typhoid fever; while T. Legry[115] concludes, with other observers, that

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[*] *Author's conclusion.*

[112] Ohlmacher: "Amer. T. B. of Pathology," p. 234, 1901.

[113] Houston: Brit. Med. Jour., Aug. 17, 1901.

[114] Constans: Brit. Med. Jour., Feb. 16, 1895.

[115] T. Legry: Gaillard's Med. Jour., Jan., 1896.

"overwork, fatigue, loss of sleep, poverty, immoderate exercise, play a very important part" in the development of sporadic cases and epidemics.

That the colon bacillus may become pathogenic under the circumstances mentioned is suggested by the marked influence of general adynamia upon the virulence of the pneumococcus, although in the case of the latter germ, the pathogenicity is due to its rapid multiplication.

Some of the morbid phenomena enumerated are but manifestations of a violent reaction of the body's protective resources.[*] The fact that animals may be immunized by gradually increased doses of living or dead typhoid bacilli and that they are now known to cause the appearance of a bacteriolytic and antitoxic substance in their blood, points clearly to the identity of the organs stimulated by the typhoid toxin or endotoxin: those of the adrenal system, through the test-organ.[*] Hence the marked febrile process, which continues until the pathogenic organisms—living and dead—and their toxins or endotoxins are destroyed.[*]

The energy with which the protective functions are stimulated by the typhoid toxins or endotoxins is well shown by the marked localized leucocytosis evoked in favorable cases.[*] The swelling of the intestinal lymphoid follicles is in fact greatly due to the presence therein of an enormous number of phagocytic endothelioid cells. This is an important feature of the prognosis of these cases, since the efficiency of the defensive process depends greatly upon the power of the small and large phagocytes—microphages and macrophages—to offset the multiplication of the typhoid germs. The importance of this fact is also emphasized by the identity of these follicles as barriers to general infection.[*]

The protective vaccinations used during the war in South Africa by Sir A. E. Wright elucidated many of the above features; they showed clearly the reaction of the body under their influence and an increase of what he terms the "bacteriotropic substances"—which, as I have shown, is composed of the aggregate of bodies which make up auto-antitoxin.

As to the localized leucocytosis, Ohlmacher[129] writes: "From the more recent and precise histological studies, especially those by Mallory, it appears that the tumefaction of the intestinal, mesenteric and splenic lymph-apparatus is due to the excessive proliferation of the phagocytic endothelioid cells arising from the lymph-spaces, lymph-vessels and endothelial layers of the blood-vessels. These cells are diffusely scattered throughout the swollen follicles and glands in immense numbers, or accumulated in large groups, and they manifest pronounced phagocytic activity, as well as multiplication or retrogressive changes."

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[*] *Author's conclusion.*

[129] Ohlmacher: *Loc. cit.*, p. [illegible].

If the phagocytes—both small and large, the latter (the macrophages) ingesting the former when bacteria-laden—succeed in ridding the lymphoid follicles of the pathogenic germs, a feature of the average case which occurs about the eighth or *tenth day*, *resolution* occurs. The amœboid cells collect the local detritus and remove it and the lymphoid elements resume their normal functions.

When, however, such is not the case, both the small and large phagocytes, either because of excessively rapid multiplication of the bacilli, or inability of the phagocytic cells to digest them* (through deficiency of the digestive agent—the auto-antitoxin—they contain), and also the epithelial elements, become necrotic, and *sloughing* occurs; a grayish mass of cellular detritus is then formed which becomes detached. This usually carries the case to the end of the *third week*. The detached slough leaves a dangerous feature of the lesions, however, viz., a round or elliptical ulcer occupying a solitary follicle or a portion of a Peyer's patch which may reach down to the muscular layer and even through to the serous coat. It may also give rise to *intestinal hæmorrhage*, owing to erosion of an artery or vein; or perforation of the intestinal wall may be followed by peritonitis, a condition which may also be brought about by extension of the inflammatory process in the lymphoid tissues.

Resolution of the ulcerated areas begins—provided the reparative functions be adequate—as soon as the slough has fallen off, new epithelium growing into the area from its periphery. Fortunately, the cicatricial tissue formed is longitudinally disposed, and does not, therefore, tend to cause constriction of the corresponding portion of the intestinal canal. The healing process terminates the fever.

This differs only from the usual version in that the all-importance of the phagocytes is emphasized. It is not deemed necessary, therefore, to adduce evidence.

Treatment.—The cardinal indication suggests itself in the light of the foregoing facts, viz., to enhance not only the bacteriolytic powers of the blood as soon as possible, but to charge it simultaneously with thyroidase (opsonin) in order to sensitize the bacteria and activate their ingestion and digestion by the phagocytes.*

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* *Author's conclusion.*

The first step in this direction is accomplished by administering—when the patient is first seen, and even where the diagnosis is not certain—*calomel* in 5-grain (0.3 gm.) doses every three hours until green liquid stools occur. Biliverdin, which gives the passages this color, being mainly composed of reduced adrenoxidase,* these stools indicate that an active bacteriolytic and antitoxic process has been provoked both in the liver and intestine. It does not show, however, that the latter has been rid of the pathogenic germs it contains,* and inasmuch as dead typhoid bacilli are pathogenic, the intestinal canal should be cleared of them by provoking a flow of intestinal fluid (which contains auto-antitoxin) through it, by means of a saline purgative—either a bottle of *citrate of magnesia* or a dose of *Epsom salts*. Violent saline purgation should be avoided, however, since it depletes too freely the blood of serum and of adrenoxidase, and reduces, therefore, its defensive properties.*

Calomel has an excellent record in the treatment of typhoid fever. Liebermeister, Bouchard and other equally prominent authorities have placed it first in the list of our resources. It has also formed the foundation of various methods which have shown a low mortality, even though its effects were hampered by the addition of intestinal "antiseptics" and other injudicious combinations. The value of Kalb's method to abort typhoid fever by mercurial innunctions in cases seen before the ninth day, was confirmed by Bartlett[117] and others. In Bartlett's cases the temperature fell to normal on the third day of treatment, and all symptoms had disappeared by the sixth. J. C. Wilson[118] treated systematically five cases by means of hypodermic injections of calomel. The cases were all severe, and all recovered. Three of them ran an exceptionally favorable course. The author concluded that calomel thus introduced into the organism exerts a decided therapeutic influence in ameliorating the symptoms and in modifying the temperature range in enteric fever. Andrievsky[119] conducted a series of experiments to determine the value of calomel. In 71 cases calomel was given in a dose of 30 grams (4 gr.) thrice daily, while for the purpose of comparison quinine was given in the same doses in 40 other cases. The patients in the first group continued to take the calomel till their evening temperature became normal; this result was obtained after a total amount of the drug, varying from 8 to 20 grams (2 to 5 drachms), had been taken. Stomatitis never occurred, nor was diarrhœa aggravated. The disease in all these patients was mild in type and often aborted. The fever abated more quickly, and the mortality (2.82 per cent.) was less than in the cases treated with quinine. No patient who was put on the calomel treatment within the first week of the illness, died. After using it in 90 cases, C. H. Lewis[130] concluded that calomel was the most useful agent at our disposal. Bettman,[131] who concludes in the same vein, gave calomel hourly in $^1/_{12}$-grain (0.0055 gm.) doses as much as twelve days before salivation appeared, a sign that these cases show considerable toleration. Hackett,[132] who regards mercury as a specific in typhoid fever (blue mass to point of toleration and an alkaline every morning), reached a similar conclusion. A large number of authors recommended calomel.

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* *Author's conclusion.*

[117] Bartlett: Australasian Med. Gaz., Nov., 1898.

[118] J. C. Wilson: Trans. Assoc. of Amer. Phys., vol. iii, p. 169, 1888.

[119] Andrievsky: La semaine méd., Dec. 28, 1896.

The larger preliminary doses and the saline purgative should be followed by *small doses,* $^1/_{10}$ grain (0.0065 gm.), of *calomel* every three hours to sustain and enhance the functional activity of the adrenal system.* This may be continued until salivation appears, when the intervals between the doses may be increased sufficiently to keep its action just within this symptom, which shows that the limit of safety has been reached.

The second indication, namely, to sensitize (opsonize) the bacilli and facilitate their ingestion by phagocytes, is not satisfactorily met by mercury;* it must, therefore, be brought about through another agent such as *thyroid gland,* which contributes thyroidase (opsonin) to the blood.* Its use with mercury would offer some danger, however, since it might coincide with the presence of an amount of thyroidase almost sufficient to sensitize the depressor nerve and thus inhibit the functional activity of the adrenal system*—an undesirable result. Iodine and the iodides are preferable. Given with mercury, ½ grain (0.033 gm.) of *iodine* and 5 grains (0.3 gm.) of *potassium iodide* night and morning, are sufficient to insure adequate sensitization of all pathogenic elements.* In cases in which the mercurials cannot be used, iodine and the iodides can be used alone, as shown below. In that case, however, *thyroid gland* will prove more active, 1 grain (0.06 gm.) three times daily being sufficient to increase markedly the blood's defensive properties.

Iodine, recommended by Sauer in 1840, has likewise been considered a "specific" in typhoid fever. Klietsch,[133] for example, after using a combination of potassium iodide and iodine in 81 cases, had but two deaths, one caused by perforation due to a dietetic error, the other from meningitis. These results were obtained during an epidemic, and were considerably better than those obtained by him during the same epidemic in 40 cases treated by the standard method—cold baths. Cavazsani[124] reported 62 cases. He began with a calomel purge, followed it up with sulphate of sodium and then the iodine, giving twenty drops (adults) of a solution containing 7½ grains (0.5 gm.) of iodine, 70 grains (4.6 gm.) of potassium iodide, in divided doses daily. He found that this treatment not only gave better results than any other, but that the complications were less frequent, that the temperature was rapidly reduced and finally that the convalescence period was considerably shorter than is usually the case. Ceriolo,[125] who practices in a region in which the disease is endemic and always severe, states that since he has been using iodine systematically, all his cases remained mild—even those which had shown a stormy onset.

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* *Author's conclusion.*

[130] C. H. Lewis: Med. Record, Aug. 2, 1902.

[131] Bettman: Cincinnati Lancet-Clinic, June 25, 1898.

[132] Hackett: Medical Record, Oct. 15, 1904.

[133] Klietsch: Münch. med. Woch., Bd. xxxix, S. 835, 1892.

A method of the utmost importance in typhoid fever, as in all febrile diseases, is the use of *saline solution from the outset* to preserve the osmotic properties of the body fluids, and, therefore, the efficiency of the defensive functions.* Even though the blood be rich in auto-antitoxin, abnormal viscidity of the blood itself, and especially of the lymph, prevents its action on germs and the poisons derived from them. The reader is referred to the general article on page 1367 for the necessary details.

The *diet* though nutritious and sustaining should provide for the fact that the intestine is the seat of lesions which render the use of foods that impose physical irritation or undue peristaltic action upon the organ dangerous, in that they tend to promote local complications.

The prevailing custom is to await hæmorrhage or the practical collapse of the patient before using the saline solution. As shown in the article referred to, this is based upon the prevailing lack of appreciation of the importance of the inorganic salts upon all functions, and particularly upon the defensive functions. Acting upon my conclusions to this effect, published in 1903, Todd[126] used saline solution from the outset and found that it kept the tongue moist—the dry, parched tongue indicating deficiency of fluids and alkaline salts—and that the course of the disease was generally improved. The important feature of his observation, however, is that he found that saline beverages proved as effective, used in the following way: Ten grains (0.6 gm.) of sodium chloride and 5 grains (0.3 gm.) of potassium bicarbonate added to 8 ounces (236 gm.) of water; a teaspoonful of lemon juice is added, which produces a mild effervescence and renders the drink very palatable. J. Madison Taylor found that the ordinary decinormal gave equally satisfactory results used as a beverage. The cardinal indication is to insure an adequate intake of this fluid to replace as much as needed of the half-ounce (15 gm.) of sodium chloride voided every day with the urine and other excretions, and which is not replaced when the diet is low.

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* *Author's conclusion.*

[124] Cavassani: Riforma medica, June 5 and 6, 1909.

[125] Ceriolo: Gazzeta degli Ospedali, vol. xxvi, p. 74, 1905.

[126] Todd: Medical Record, Apr. 14, 1906.

As to the use of *cold baths*, they are not necessary if the foregoing measures are carried out. *Sponging* is useful, however, when the temperature—a manifestation of the curative process—exceeds 103° F. (39.5° C.), to enhance the dissipation of heat from the skin.

Cardiac failure which usually occurs late in the disease and even during convalescence, and is attended by increased prostration, low blood-pressure, hypothermia, sweating and weak, rapid and even irregular pulse is in reality due to *adrenal failure*. In such cases, an intramuscular injection of 8 minims (0.5 gm.) of *adrenalin* 1:1000 solution, repeated as needed often saves life.

If *hæmorrhage* occur, the aim should be to cause constriction of the intestinal arterioles;* we have seen that *morphine* produces this effect. Its value is shown by the fact that it is generally employed in this identical condition. *Constipation* is best met by means of large enemas of warm saline solution.

Prophylaxis.—The influence of excessive fatigue, a predisposing cause in the epidemics observed in troops during arduous campaigns,* should be borne in mind, in view of the likelihood that the bacillus coli can assume the virulence of the typhoid bacillus.* Proper periods of rest and increased transportation facilities will obviate this danger. An important feature of this question is that "excessive fatigue" means in this connection, abnormal consumption of adrenoxidase, nucleoproteid and of the zymogens which jointly sustain metabolism—the identical substances of which auto-antitoxin is composed.* The use of agents such as *quinine* or *coffee*, which stimulate the adrenal and vasomotor centers, is therefore indicated.* Prophylactic *vaccination* during the World War reduced the incidence of typhoid fever in troops to a negligible proportion. In the French army two injections per man reduced it to 0.3 per 100,000 men. This is due from my viewpoint, as we have seen, to stimulation of the endocrines.

In civil life, *thyroid gland*, 1 grain (0.06 gm.) and *quinine*, 2 grains (0.13 gm.) may protect, when there is a likelihood of infection or even when the premonitory symptoms of the disease have occurred. Thyroid gland, by increasing powerfully the bacteriolytic power of the blood, and quinine hydrochlorate, by driving the blood towards the capillaries, cause the intestinal mucosa and its lymphoid follicles to become congested with blood rich in protective properties, while the digestive activity of the phagocytes is also increased. Both the blood and its cells being likewise fully supplied with thyroidase, pathogenic germs are readily sensitized, thus augmenting greatly their vulnerability to destruction by the phagocytes.

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* *Author's conclusion.*

Iodine and the *iodides* can also be combined with quinine, preferably the *quinine hydrochlorate.* None of the other agents of our pharmacopœia are sufficiently active to afford adequate protection.[*]

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[*] *Author's conclusion.*

CHAPTER XXXI.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

THE ADRENAL SYSTEM IN DISEASES OF THE BLOOD.

The pathogenesis of the "anæmias" is considerably elucidated by the views and evidence I submit in the present volume. In true anæmia, the fact that the adrenal system governs the proportion of adrenoxidase—oxyhæmoglobin—that the blood contains, at once imposes itself as an important feature of the problem, especially in view of the purpose I have ascribed to the iron-laden hæmatin, viz., to anchor this oxidizing substance in the red corpuscles pending its distribution to the tissues. The pathogenesis of the disease, as I conceive it—absence of iron to hold the oxyhæmoglobin (adrenoxidase) and insufficiency of the latter through depressed activity of the adrenal system—becomes self-evident. In pernicious anæmia, the exaggerated hæmolysis finds as ready an explanation in an excess of auto-antitoxin in the blood through overactivity of the adrenal system, excited by autotoxins derived from food and tissue-wastes. In chlorosis we have a more complicated order of phenomena: marked hypoactivity of the adrenal system, and, as a result, general vasodilation and ischæmia of the peripheral vessels. The general vascular relaxation entails another important pathogenic feature, however: inadequate circulation of the blood in the hepatic capillaries, and therefore imperfect assimilation of iron, a function in which the liver plays a cardinal rôle. Finally, in hæmophilia, we have an example of congenital hypoactivity of the adrenal system. This entails a constant deficiency of adrenoxidase in the blood, and since adrenoxidase is the fibrin ferment, the coagulative properties of the blood are very deficient; it preserves its fluidity even when a vessel is ruptured therefore, and flows from the vessel as if it were water.

ANÆMIA.

Definition.—Anæmia, a disorder characterized by pallor, in which the red corpuscles may or may not be destroyed, may be brought on by several morbid conditions, the most prominent of which are: a deficiency in the corpuscular hæmatin, of the iron which anchors the adrenoxidase (oxyhæmoglobin) in the red corpuscles pending its distribution to the tissues; hypoactivity of the adrenal system and the resulting general vasodilation, a condition which entails an accumulation of blood in the splanchnic area and ischæmia of the cutaneous capillaries.*

Symptomatology, Pathology and Pathogenesis.—Some pallor of the skin and mucous membranes, with perhaps slight dyspnœa, and a tendency to become fatigued without undue exertion, constitute the entire symptomatology of mild cases. In more advanced or grave cases, the pallor may become very marked; the mucous membranes, especially those of the fauces and gums, being almost blanched. There is mental and physical depression and a marked tendency to indolence. "Palpitations," faintness, irritability, neuralgia, anorexia, indigestion, dyspnœa on exertion, headache, disorders of menstruation, and constipation are common phenomena. There is general hypothermia of the periphery, the hands and feet being usually cold. The pulse is often rapid, large and soft, though no fever be present. The specific gravity of the urine is low, and the urea excreted may be considerably below normal. Œdema, especially of the ankles, is occasionally observed. Physical examination in severe cases usually elicits the fact that the heart is dilated, and a venous hum in the veins of the neck, coupled with a systolic bellows murmur over the carotid arteries, is frequently heard. In some instances, a systolic murmur may be detected over the aorta and pulmonary artery.

These phenomena may be said to represent the aggregate symptomatology—as to main signs—of the various forms of benign anæmia. In some instances but few of these signs appear; in others the entire symptom-complex is very marked.

Examination of the blood may reveal no diminution of the red corpuscles, or of the hæmoglobin. But this is a *spurious* or *pseudo-anæmia*, the result of relaxation of the vascular system and accumulation of the blood in the great central vessels at the expense of that in the peripheral capillaries. This condition, due to depression of the vasomotor center, such as that produced by chloral, the bromides (*q.v.*), etc., is generally observed in nervous disorders, in new-comers in tropical countries, and arteriosclerosis and other conditions.

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* *Author's definition.*

Ehrlich and Lazarus[1] define anæmia as "a quantitative and qualitative diminution of the amount of blood." This definition does not include, however, a morbid condition which explains many cases of benign anæmia we meet in practice, *i.e.*, those due to an accumulation of blood in the greater central blood-channels, a condition which, by depleting the peripheral capillaries, provokes pallor. Under the caption "Local Anæmia," Osler,[2] for instance, states that "local anæmia of the brain, causing swooning, ensues when the mesenteric channels, *capable of holding all the blood of the body*, are wide open." Vasomotor relaxation alone accounts for this and the sudden pallor that attends swooning proves that chronic depletion of the cutaneous vessels may be a cause of chronic pallor, which may be, and often is, taken for true anæmia. Indeed, several other characteristic symptoms of true anæmia may appear; thus dyspnœa may result from the fact that the capillaries of the air-cells likewise fail to receive sufficient blood to satisfy the needs of the body, as emphasized by J. H. White.[3] The irritability so often observed in anæmics finds an explanation in the fact that autotoxins accumulate in neural elements, including those of the brain, when the oxidation processes therein are slackened. The increase of cardiac dullness which denotes dilation, a symptom upon which F. Müller[4] lays stress, may likewise be caused by diminution of the blood supplied to the myocardium. Cohnstein and Zuntz[5] long ago attributed to vasomotor narrowing of the peripheral vessels the marked fluctuations in the number of red cells so often observed. This undoubtedly accounts for the observation of Pokrowsky[6] that the first dose of iron (which, we have seen, stimulates the vasomotor center) sometimes causes a rise of temperature—which would mean, in the light of the foregoing data, that the peripheral capillaries become richer in arterial blood.

Anæmia due to *insufficient food* likewise belongs to the category of pseudo-anæmias.* The red corpuscles not only fail to become reduced in number during periods of experimental starvation, but they are sometimes increased. The percentage of leucocytes, however, may be considerably reduced, owing to the absence of the periodical leucocytosis connected with digestion and inadequate nutrition of the leucocytogenic organs.* Since the salts of the blood, especially sodium chloride, are obtained from food, they are also deficient; the albumins are likewise diminished for the same reason. The hypothermia, coldness of the extremities, etc., observed in those cases indicate that, as in the group reviewed above, there is not only deficient general oxygenation—owing to the depressed condition of the adrenal center—but also depression of the general vasomotor center and recession of blood from the periphery to the great central mesenteric channels.[*]

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* *Author's conclusion.*

[1] Ehrlich and Lazarus: Nothnagel's "Encyclo. of Pract. Med.," Amer. ed., vol. on Dis. of Blood, p. 15, 1905.

[2] Osler: "Pract. of Med.," sixth edition, p. 712, 1905.

[3] J. H. White: Birmingham Med. Rev., Oct., 1900.

[4] Müller: Berl. klin. Woch., Bd. xxxii, S. 834, 1895.

[5] Cohnstein and Zuntz: Pflüger's Archiv, Bd. xlii, S. 303, 1888.

[6] Pokrowsky: Virchow's Archiv, Bd. xxii, S. 476, 1861.

Senator and Müller[7] observed in the fasting subjects, Cetti and Breithaupt, that in the former the number of red corpuscles was increased 1,000,000 after ten days' fast, while the leucocytes decreased from 12,000 to 4200. Referring to this and other experiments, Lazarus[8] says in this connection, "from exact experiments on man and animals, therefore, the conclusion can be drawn that sudden absolute withdrawal of nourishment is not capable of producing an anæmia." In the course of his remarks on the influence of insufficient food, he also states: "Sahli first, after him Laache, Oppenheimer and others, demonstrated that individuals with very pale skin and mucous membranes frequently showed a normal percentage of hæmoglobin and a normal number of corpuscles."

In the toxic anæmias, *i.e.*, those due to *various poisons* and to *bacterial toxins,* the vasomotor center is likewise depressed.[*] To this category belong the anæmias observed (1) in workers in lead and arsenic, (2) in chronic alcoholism and the excessive use of tobacco, (3) syphilis, malaria, malignant tumors, diphtheria, tuberculosis and helminthiasis.

In this group of anæmias, however, another morbid factor asserts itself, namely, deficient functional activity of the adrenal center, which entails a corresponding deficiency of adrenoxidase in the blood.[*] Adrenoxidase being fibrin ferment,[*] the coagulation period of the blood is lengthened. The diminution of adrenoxidase causing the quantity formed to be utilized by the blood itself and the tissues with unusual rapidity,[*] the red corpuscles, its carriers,[*] become more or less reduced in size (poikilocytosis) because they are inordinately depleted. As adrenoxidase is likewise the albuminous constituent of the hæmoglobin molecule,[*] the hæmoglobin is reduced (oligochromæmia), but less so usually than the red corpuscles themselves; since the adrenoxidase is continually being reformed through the adrenals,[*] while the red cells are diminished pathologically. The reduction of the red corpuscles (oligocythæmia) is a normal result of the deficiency of adrenoxidase—the bone-marrow being inadequately nourished,* the genesis of the cells is correspondingly inhibited. The same morbid influence naturally impairs leucocytogenesis;* if, therefore, the blood is examined between the postprandial periods of leucocytosis,* the relative percentage of leucocytes is found reduced. When this is marked, the postprandial leucocytosis is also unusually low and less food, including blood-salts, being taken up from the alimentary canal,* the alkalescence of the blood is deficient. This is shown by the increase of the blood-platelets,* a concomitant phenomenon.

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[*] *Author's conclusion.*

[7] Senator and Müller: *Ibid.*, Bd. cxxxi, Supp., 1893.

[8] Lazarus: Nothnagel's "Encyclo. of Pract. Med.," vol. on Dis. of Blood, p. 181, 1905.

The familiar paralytic phenomena of chronic lead-poisoning clearly point to the impairment of nutrition caused by lead, a function governed, we have seen, by the vascular and adrenal systems. As to arsenic, ample evidence has been submitted showing that it is the physiological antagonist of thyroidase which upholds the functional efficiency of the adrenal center. As to its influence on the vasomotor center, H. C. Wood[9] states that "arsenic greatly lessens the rate and force of the pulse-beat and markedly lowers the blood-pressure." Chronic mercurial poisoning provokes symptoms similar to those of lead, but as we will see, the anæmia here is due to hæmolysis.

As to the rôle of the vasomotor and adrenal systems in the anæmias due to various toxins, Grawitz[10] has shown that extracts of malignant growths do not, when injected into the blood, affect the red corpuscles or the hæmoglobin directly, thus proving that the anæmia is due to some indirect influence. The identity of the organ upon which this influence is produced is well shown by the observation of Loeb and Smith,[11] that the cephalic portion of ankylostoma contains a substance which *inhibits* coagulation. As adrenoxidase is the fibrin-ferment, the depressing action of the toxic substance on the adrenal center is self-evident. In the light of this fact and others previously submitted, the sequence of events recited above assumes a normal aspect.

The *anæmias due to hæmorrhage* following injuries, or from the lungs, stomach, intestines, uterus, kidneys, and ruptured aneurism, lesions of intestines due to parasites, violent epistaxis, or occurring in the course of purpura, scurvy, etc., are marked in proportion as the blood lost during a given time is great. The anæmia is rapidly developed, the face being blanched if the loss is great. This is promptly followed by great muscular weakness, weak and rapid pulse, cold sweats, coolness, especially of the extremities, dyspnœa, vertigo, fainting, weakness of the voice, tinnitus, hallucinations of smell, flashes of light and finally syncope, during which there may be delirium and convulsions, and finally, death. If, however, the hæmorrhage cease spontaneously, or be arrested before one-half of the blood in the body has been lost, recovery may ensue, the patient remaining extremely weak for some time. In less severe cases, two or three weeks suffice to complete the recovery, especially in women.

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* *Author's conclusion.*

[9] H. C. Wood: "Therapeutics," etc., eleventh edition, p. 447, 1900.

[10] Grawitz: Virchow's Archiv, Bd. lxxvi, S. 353, 1879.

[11] Loeb and Smith: Proceedings Pathol. Soc. of Phila., vol. xxv, p. 173, 1904.

After moderate hæmorrhages the liquid portion of the blood is replaced at the expense of the lymph in the tissues. As this liquid is serum, the cellular elements are alone reduced, the red cells numbering as low as 2,000,000 in these cases and below 1,000,000 after severe hæmorrhages, though the leucocytes, which are produced with great relative rapidity,* may be somewhat increased. Water being simultaneously absorbed from the alimentary canal in the more severe cases, the increase of both fluids in the blood is more rapid than that of the cells and hæmoglobin; as the case progresses, therefore, examination of the blood may suggest an unfavorable course, *i.e.*, that the cells and hæmoglobin are steadily reduced. This phenomenon is but a temporary one, however; after a few days the tide turns and uninterrupted recovery follows. This is mainly because the adrenals, of all organs, seem alone to continue their important functions uninterruptedly.* Proof of this is afforded by the facts that the blood becomes much more coagulable immediately after bleeding and that the blood-platelets are also greatly increased. Both the blood-platelets and the fibrin ferment being adrenoxidase, the manner in which the coagulability is increased is obvious.* The relative paucity of red corpuscles causes some, at least, of these cells to absorb an unusual proportion of adrenoxidase and they appear swollen.* In most cases, however, their size is somewhat reduced; they are paler than usual, and many of them are nucleated.

The leucocytosis that attends the digestive process, inflammatory processes, etc., indicates that a great relative genesis of these cells can occur physiologically as implied above. The increase of coagulability is referred to by Ehrlich and Lazarus[23] as an "important alteration which takes place immediately after the hæmorrhage, and is sometimes active in checking it. According to E. Freund's investigations," add these authors, "the time of coagulation may be hastened from nine to three minutes by hæmorrhage." Under hæmophilia we will see that this is precisely what occurs when thyroid extract is given, and that the increase of coagulability is due to an increase of fibrin-ferment, *i.e.*, of oxidase, in the blood. The fact that the fibrin ferment (adrenoxidase) and the blood-platelets are identical substances, is further sustained by the additional statement of Ehrlich and Lazarus that, as observed by Hayem, "the blood-platelets are markedly increased in post-hæmorrhagic anæmia"—concurrently, therefore, with the increased coagulating properties of the blood.

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* *Author's conclusion.*

[23] Ehrlich and Lazarus: *Loc. cit.*, p. 163, 1905.

Another important cause of anæmia, especially among the poor, is the use of *food deficient in iron*, as the only nutriment, *i.e.*, milk, bread, rice, potatoes, etc. The hæmoglobin percentage not only fluctuates according to the quantity of iron in the food, because this metal is the fundamental constituent of hæmatin (the coloring-matter of hæmoglobin), but also because it serves as binding agent between the hæmatin and the adrenoxidase (the albuminous portion of the hæmoglobin molecule) as the latter is being formed in the lungs.* Besides this cardinal function, iron is an ubiquitous component of the chromatin of nuclei, the living portion of the cell.* Hence it is also found in nucleo-proteid, the food-product from which the structural components of both hæmoglobin and chromatin are derived. Food deficient in iron produces anæmia, therefore, by reducing the proportion of hæmoglobin built up in the body; moreover, it inhibits general nutrition by impairing the molecular structure of the living substance of the tissue-cell.* This form is mainly observed among subjects who are deprived of meat and fruit, which contain enough iron to satisfy the needs of the organism.

Verdeil, in 1849, showed that the blood-ashes of dogs fed on bread showed considerable less iron than when they were fed on rich meat diet. Von Hösslin found that a diminution of iron in food and not of the albumin altered the composition of the blood, and particularly its hæmoglobin, an observation confirmed by Bunge, Kunkel and others.[13] Bunge[14] and Häusermann[15] also showed that very few articles of food (egg-albumin, rice, pearl-barley and wheat flour) contained less iron than milk, *i.e.*, 2.3 milligrams to 100 grams, a fact recently confirmed by Schmey.[16] In the case of an adult who lived exclusively on milk, observed by Häusermann, the number of corpuscles was normal, but the percentage of hæmoglobin was reduced to 60 per cent.

That the chromatin (living substance*) of nuclei contains iron was shown by Bunge and Macallum[17] in animals and plants, including those, of course, which are used as foods. But this fact in itself proves that our own chromatin contains iron, and that food deficient in this element must impair not only the hæmoglobin-forming process, but also the vitality of our tissues—including that of all the nerve-centers—as shown by experimental and clinical evidence.

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* *Author's conclusion.*

[13] Bunge, Kunkel and others: Cited by Ehrlich and Lazarus: *Loc. cit.*, p. 132, 1905.

[14] Bunge: Zeit. f. physiol. Chemie, Bd. xvi, S. 174, 1891.

[15] Häusermann: *Ibid.*, Bd. xxiii, S. 506, 1897.

[16] Schmey: Hoppe-Seyler's Zeit., Bd. xxxix, S. 215, 1903.

[17] Macallum: Jour. of Physiol., vol. xvi, p. 268, 1894, and Reports of Brit. Assoc. for Adv. of Sci., 1896.

Treatment.—*Iron* is used promiscuously in anæmia; but the foregoing groups indicate that in the majority of instances, its administration will prove futile unless the cause of the blood-disorder be eliminated.

The only exception is the form of anæmia due to *food deficient in iron,* in which this metal, coupled with a diet richer in this metal than the patient's usual food, will prove beneficial without other remedies. Blaud's pill, one three times daily for a week, then increased by one pill daily until three pills are taken after each meal, and the addition of beef, eggs (the yolk of which is rich in iron), spinach, asparagus and fruit, especially apples, insure recovery, especially if the patient is able to spend a few weeks at the sea-shore or in the mountains. Unfortunately, a change of diet of this kind is inaccessible to the majority of cases, since this form of anæmia occurs mainly among the poor. Here, however, spinach, which is twice as rich as beef in iron, green cabbage leaves prepared in various ways, and which contain as much iron as lean beef, may be added to the customary diet. White beans, carrots and wheat-bran are inexpensive, but contain more iron than potatoes or any of the porridge cereals. Ferratin, or the dried sulphate of iron, may be used advantageously in the rare cases in which Blaud's pill is not well borne.

The tincture of the chloride of iron so often used is not a good remedy. It tends to provoke constipation. The majority of cases in which iron proves valueless are instances of erroneous diagnosis, in which the anæmia is due to active destruction of the red cells, *i.e.*, hæmolysis. Such cases may rapidly grow worse under the influence of iron. Barnes recommends a neutral odorless and tasteless solution he terms iron vitellin. Murrell,[10] in a clinical study of various forms of iron, including Blaud's pill, found that the dried sulphate gave the best results among the inorganic preparations, while iron vitellin, of all the organic preparations, not only proved the most active, but also 50 per cent. more so as to red corpuscles and 25 per cent. as to hæmoglobin, than the best inorganic iron.

In the *toxic anæmias,* the first indication, of course, is to eliminate the causative poisons, extrinsic or intrinsic, *i.e.*, those which are depressing the vasomotor and adreno-thyroid centers.[9]

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[9] *Author's conclusion.*

[10] Murrell: Medical Press, July 6, 1904.

In workers in lead, *potassium iodide*, given in increasing doses after meals, and in large quantities of water, is of recognized value; these salts stimulate powerfully the adreno-thyroid center, and secondarily the vasomotor center.* In arsenic anæmia, *thyroid gland* is indicated,* since arsenic and thyroidase are physiological antagonists, the latter being the normal stimulant of the test-organ.* In the anæmia of alcoholism or nicotinism, cessation of the use of alcohol and tobacco is sufficient, since alcohol robs the blood of its oxygen directly, while nicotine is a vasomotor depressant.* In syphilis, the *iodides* or *mercury* come first in order after thyroid extract,* while in the anæmia due to malaria, *quinine*, as an activo stimulant of the vasomotor and adrenal systems, is of especial value.

The relationship between arsenic and thyroid extract is based on the observation of Bédart and Mabille,[19] confirmed by Ewald,[20] that the untoward phenomena caused by iodothyrin could be reduced and even prevented by the simultaneous use of arsenic.

In the post-hæmorrhagic form, no remedies are required. A copious diet and fresh air soon cause the blood to resume its normal condition. The process may be hastened, if necessary, by means of small doses of *thyroid gland*, 1 grain (0.06 gm.) after each meal.

PERNICIOUS ANÆMIA.

SYNONYMS.—*Progressive Pernicious Anæmia; Idiopathic Anæmia.*

Definition.—Pernicious anæmia, a disease of the blood characterized by extreme pallor and a marked reduction of the red corpuscles, is due to the presence in the blood of toxic substances which, by overstimulating the test-organ, keep the blood sufficiently overladen with auto-antitoxin to produce progressive hæmolysis.**

Symptoms and Pathology.—The most prominent symptom is extreme pallor, both face and body gradually assuming a lemon-yellow tint. The yellowish color usually deepens as the case progresses, but it may appear suddenly. In contrast with this hue is the blanched appearance of the membranes, the mouth, lips and gums.

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* *Author's conclusion.*

** *Author's definition.*

[19] Bédart and Mabille: C. r. de la Soc. de biol., 10 série, vol. v, p. [illegible], 1898.

[20] Ewald: Die Therapie der Gegenwart, Sept., [illegible].

The blood is correspondingly pale and watery. Examination reveals a very marked reduction of the red blood corpuscles. While normally the proportion is about 5,000,000 to the cubic millimeter, it may be reduced in this disease to below 500,000, and even to a lower ratio. Quincke reported a case in which there were only 143,000 immediately before death. While the hæmoglobin is also reduced, the ratio of this pigment to the blood corpuscles is higher than usual. This is an effort at compensation, and proves again that the red corpuscles are but storage cells for oxyhæmoglobin.[*] Many of the corpuscles become greatly enlarged, being then termed *megalocytes.* Some are irregular in shape, *i.e., poikilocytes,* while others again may be smaller than usual: *microcytes;* but neither of these two modifications of shape is pathognomonic. Nucleated red corpuscles are almost always found, however, the normal-sized *normoblasts,* the nucleus of which is markedly stained, and the large *megaloblasts* with pale nuclei.

The onset of pernicious anæmia is gradual and insidious. Weariness and weakness increase until the patient reaches a state of extreme debility, with marked tendency to vertigo and fainting. Numbness beginning at the extremities, weakness or absence of tendon reflexes, and paralysis are sometimes witnessed. Dyspnœa on exertion and sighing are also prominent features. And yet, no emaciation occurs.

These phenomena are generally ascribed to a gradual destruction of the red corpuscles. This view is sustained and elucidated by the functions of the adrenal system. A connection between this disease and the adrenals was suggested by Addison in 1855.

The adrenoxidase, of which the red corpuscles are the carriers, being one of the triad that insures the functional efficiency of all tissues,[*] reduction of the number of red corpuscles correspondingly reduces the volume of this substance. As the muscles constitute the bulk of the body tissues, progressive weakness is the most prominent sign. This explains also the paræsthesia, loss of tendon reflex, and paralysis. The tendency to fainting is due to a similar condition of the brain cells. The dyspnœa and sighing are characteristic signs of inadequate tissue oxygenation. The absence of emaciation is ascribable to the fact that the leucocytes, which supply the nutrient granules to the tissues, are not destroyed concurrently with the red corpuscles.[*]

The cardio-vascular symptoms are very marked. The pulse is rapid and large, but soft, and sometimes jerky. The arteries and veins may pulsate and throb visibly. A loud venous hum can usually be detected, with the stethoscope, in the vessels of the neck. Cardiac murmurs may also be heard. The blood coagulates slowly. Retinal hæmorrhage is frequently observed; epistaxis, menorrhagia, purpuric eruptions, and cerebral hæmorrhage may occur. Œdema of the ankles, face, and lungs, and dropsical effusions may appear at any stage.

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[*] *Author's conclusion.*

These are all manifestations of two conjoined factors: general vascular dilation and the diminution, in the blood, of fibrin ferment, *i.e.*, adrenoxidase.* The vascular dilation is due to relaxation of the muscular coat of all vessels incident upon lowered oxygenation of the vessel walls. As a result, and in accord with Marey's law, the pulse rate is increased. The relaxation of the vascular walls facilitates penetration of the blood-plasma wherever hypostatic congestion occurs; hence the œdema. The adrenoxidase being the fibrin ferment which converts fibrinogen into fibrin, the coagulating power of the blood is impaired and the hæmophilic state is initiated.* This, added to the watery condition of the blood, provokes the hæmorrhagic phenomena.*

Gastric and intestinal disorders are the rule. There is indisposition to eat and disgust for food, rather than true anorexia. Indigestion, nausea, vomiting, and diarrhœa are frequently observed. The gastric juice is generally deficient in hydrochloric acid.

The activity of all the gastric functions, muscular and secretory, is primarily lowered owing to the inadequate supply of adrenoxidase, which destruction of the red cells entails. The peristaltic action of the walls of the stomach being imperfect, the food undergoes correspondingly deficient preparatory digestion, a morbid process aggravated by the fact that pepsinogen, nucleo-proteid and adrenoxidase, the three active factors of gastric juice, are not secreted in sufficient quantities.* The deficiency of hydrochloric acid shows that such is the case. The concurrent relaxation of the cardiac and pyloric muscular fibers allows the imperfectly digested food to penetrate the intestines, where it meets correspondingly impaired muscular and secretory functions. The succus entericus is deficient in auto-antitoxin, hence the presence of gastro-intestinal disorders.*

The liver, kidneys and spleen show an increase of iron pigment. In the liver it is usually found in great quantities in the lobules and the bile capillaries. The urine, on the other hand, may be pale, but it often contains urobilin and is dark.

Both the iron and the urobilin are products of broken-down red corpuscles. The iron which passes to the intestines with the bile is usually recovered by the intestinal leucocytes* and utilized in the reconstruction of hæmoglobin. The decrease of red corpuscles limiting the use of all the iron, the surplus accumulates in the various organs mentioned. Considerable adrenoxidase may also be wasted; this substance and urobilin being identical bodies, it darkens the urine when oxidized, precisely as it does in the skin when bronzing occurs.* Bronzing is also observed sometimes in pernicious anæmia.

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* *Author's conclusion.*

Etiology and Pathogenesis.—Repeated parturition is a predisposing factor in many cases, the disease being seldom encountered in primiparæ. Prolonged and immoderate lactation also appear as precursors in a small proportion of cases. Both in men and women, malaria, syphilis, purulent foci, especially pyorrhœa alveolaris; septicæmia, gastric ulcer, etc., are included among the causative intoxications. The imperfectly digested food-stuffs that remain in the gastro-intestinal canal, as explained under the previous heading, or intestinal disorders provoked by intestinal parasites, also act as foci for a practically continuous auto-intoxication.

The disease is due to the presence in the blood of any poisonous substance generated directly or indirectly through any one of these morbid conditions, and to the irritating influence of this poison upon the test-organ.* The adreno-thyroid center being overstimulated, a sufficient excess of auto-antitoxin is present in the blood* to destroy the red corpuscles more or less actively, *i.e.*, to cause hæmolysis.

The fact that the blood contains a substance which destroys the red corpuscles in this disease, as shown by Bordet and also Ehrlich, who termed it "hæmolysin," is now generally recognized. The nature of the substance, however, has remained obscure. As shown above, the process is readily accounted for through excessive functional activity of the adrenal system, the auto-antitoxin including also, as I have shown, the iodine-laden thyroidase which contributes markedly to the destructive process.

The excessive functional activity of the anterior pituitary, *i.e.*, of the test-organ, in this disease, is well shown by the fact that in pregnancy—a frequent cause of the disease—the organ is always overactive, being kept so, we have seen, by the excess of toxic wastes which the fœtus contributes to the maternal blood. In 1898 Comte[51] examined histologically the pituitary of a number of women who had died during pregnancy, and found the anterior pituitary hypertrophied in every case. This was confirmed by Launois and Mulon.[52] Douglas Stanley[53] found marked lesions in the adrenals in a case of pernicious anæmia. The excessive activity of the adrenals, by causing an overproduction of adrenoxidase, increases correspondingly the oxidizing power of the blood. In the liver, where the temperature is higher than elsewhere, the proteolytic activity of the blood is raised beyond the resisting power of the red corpuscles, and those cells are destroyed (hæmolysis)* in this organ with greater rapidity than in the general blood-stream. Colman,[54] after a study of 22 cases, concluded, in fact, that the disease was essentially due to a destruction of these cells in the liver. The disease was attributed to hæmolysis by Quincke, thirty years ago, his opinion being based on the marked accumulation of iron in the liver. This view has been accepted by most observers, and is now the prevailing one, as already stated.

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* *Author's conclusion.*

[51] Comte: Thèse de Lausanne, 1898.

[52] Launois and Mulon: Ann. de gynéc. et d'obstét., 2 série, vol. 1, p. 2, 1904.

[53] Douglas Stanley: Brit. Med. Jour., Feb. 16, [illegible].

[54] Colman: Edinburgh Med. Jour., Mar. and Apr., 1901.

Treatment.—In true pernicious anæmia, iron is obviously useless, since it merely adds to that already accumulated in large quantities in the liver and other organs.

Arsenic—which acts by depressing the excessive activity of the test-organ, *i.e.*, the adrenal system, reducing thereby the proportion of the auto-antitoxin to which the hæmolysis is due—has proven of real value, but only when given in comparatively large doses. Beginning with 5 minims of Fowler's solution, the dose should be increased at the rate of 1 minim (0.06 gm.) each day, until 30 minims (2 gms.) are administered three times a day. It should be persisted in for months, with intermissions of a few days, but only if necessary; and in all cases its use should go hand in hand with repeated examinations of the blood. The recovery, as previously stated, is often ephemeral. The case should be closely watched at least two years after disappearance of the morbid symptoms, and the use of the remedy resumed as soon as any indication of recurrence, as shown by blood count at intervals, appears. Sodium cacodylate is suitable for hypodermic use, $^1/_2$ grain (0.033 gm.) being injected three times daily.

The beneficial action of arsenic is readily accounted for when its depressing influence on the adrenal system is taken into account, as above.[*] Bédart and Mabille[illegible] found that arsenic counteracted all the morbid effects of thyroid medication, a fact confirmed by Ewald[illegible] and others. In pernicious anemia, therefore, it diminishes the production of auto-antitoxin and thus arrests the hæmolytic process.[*]

Antiseptics have been advocated to counteract the auto-intoxication engendered by the putrefactive contents of the gastro-intestinal canal. *Salol,* 10 to 15 grains (0.6 to 1 gm.), in capsules, three times a day, or *betanaphthol,* 2 grains (0.13 gm.), in pills, twice or thrice daily, have each given satisfactory results occasionally, particularly in cases in which arsenic could not be used, or had to be discontinued. *Lavage of the stomach* and enemata of *normal saline solution* have also been used, mainly to remove accumulations of undigested food-stuffs. They do more, however; the saline solution being partly absorbed, the osmotic properties of the blood, which are impaired by the continuous overactivity of the adrenal system, are improved.* Enemata plus subcutaneous injections of saline solution and arsenic are very efficient.

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[*] *Author's conclusion.*

[illegible] Bédart and Mabille: *Loc. cit.*

[illegible] Ewald: *Loc. cit.*

Finely powdered *bismuth subnitrate,* in 10-grain (0.6 gm.) doses, twenty minutes before meals, is a far better antiseptic than either of the above.* It is slowly absorbed, and counteracts gastro-intestinal irritation. If an impure salt happens to be taken, the contaminating agent is arsenic—which cannot but enhance its beneficial effects.

Salol on reaching the alkaline intestinal juice splits into salicylic acid and carbolic acid. The latter anæsthetizes the gastro-intestinal mucous membrane, but, with the salicylic acid, disinfects putrefactive contents. Beta-naphthol also dulls the sensibility of the canal, retards digestion, acting similarly *in vitro;* and is likewise a disinfectant. Hence both remedies may aggravate the gastro-intestinal disorder, but their antiseptic properties prove beneficial when the intestinal contents happen to be very toxic.*

As to the use of saline solution, Alex. McPhedran[11] relates the case of a man, aged 55 years, in whom the blood-count showed 480,000 per cubic millimeter; hæmoglobin, 20 per cent. There was delirium, vomiting and diarrhœa. Treatment by subcutaneous injections of normal saline solution on every alternate day, and the intervening of saline enemata, with arsenic internally. The patient, at the time of the report, was practically well.

Various other sources of intoxication must be antagonized. The presence of pyorrhœa alveolaris, considered by Hunter as a prominent source of auto-intoxication, imposes the use of antiseptic mouth washes and dentifrices. Useful for this purpose, after cleansing the teeth, is the following preparation:—

Fl. ext. of hamamelis .... ʒij (8 gm.).
Alcohol,
Rose water, of each .... ℥ss (15 gm.).

Apply to the gums with a cotton wad after carefully cleansing the teeth following each meal.

Some clinicians emphasize the need of rest in an armchair or in bed, relapses having been known to follow fatigue, *i.e.*, muscular exertion. A light nutritious diet is also recommended.

A *milk diet* is a valuable measure in this connection. Practically no waste-products being formed by this food, the adrenal system, subdued directly by the arsenic and indirectly by the bismuth and the oral hygiene, soon loses its overactivity, and ceases to produce the excess of adrenoxidase to which the destruction of red corpuscles is due.

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* *Author's conclusion.*

[11] Alex. McPhedran: Canadian Pract., Nov., 1897.

G. L. Gulland[33] lays special stress on diet in the treatment of pernicious anæmia. This should be arranged with care to suit each case, but the broad principles are that, as long as the blood-count is low, it should consist entirely of milk and farinaceous food; no meat of any kind should be permitted. Of course, this change of diet partly meets the second indication, the diminution of bacterial processes in the intestine. It is not uncommon to find that patients when they are first seen have large quantities of indican and similar substances in the urine, and that after a week or two on a farinaceous diet these practically disappear.

Muscular exertion entails the production of wastes which must be converted in the blood into eliminable end-products. This means overactivity of the adrenal system and, therefore, increased destruction of red corpuscles.* The same untoward effect is provoked when meats are allowed. Their conversion into assimilable granules is imperfectly performed and toxic wastes also unduly excite the adrenal system, thus aggravating the morbid process.*

CHLOROSIS.

Synonyms.—*Green Sickness; Chloranæmia; Chloræmia; Morbus Virgineus.*

Definition.—Chlorosis, a form of anæmia characterized by a yellowish or greenish tinge of the skin, and occurring usually in young girls, is due to the presence of three concurrent morbid factors: (1) depressed functional activity of the adrenal system; (2) inadequate assimilation of the iron from food-stuffs; and (3) marked diminution of the iron-laden hæmatin which holds the adrenoxidase in the red corpuscles pending its distribution to the tissues.**

Symptomatology and Pathology.—The most striking symptom of this disease is a yellowish-green hue of the skin, lips, conjunctiva and all mucous membranes, coinciding with an absence of emaciation. In a small proportion of cases, however, the blood-changes observed in chlorosis appear irrespective of these objective phenomena, the face being normal as to color and the cheeks rosy. The patient may, in fact, show some tendency to adiposis. Even in these instances, however, as in the typical cases, there is marked weakness, lassitude and indisposition to exertion. The appetite is either greatly reduced, or capricious, the patient longing for pickles, vinegar, etc., and ingesting such articles as chalk, slate pencils, soil, etc. Enteroptosis, gastroptosis, hyperchlorhydria, gastrodynia (due in some cases to gastric ulcer), and movable kidneys are commonly observed. Constipation is almost the rule. Dyspnœa, palpitations, sometimes accompanied with some irregularity in the heart's action, though the pulse be large and soft, are frequently noted, along with purely functional cardiac murmurs, usually located at the base, and sometimes at the apex, when the heart is markedly dilated. The murmurs may often be traced up along the vessels of the neck. Along the course of the jugular vein, especially on the right side, a peculiar venous hum, the "bruit du diable," is also discernible in over one-half of the cases. Neuralgia, vertigo, fainting, moroseness, and hysterical phenomena are not uncommon, especially in young girls, who constitute the great majority of cases. The eyes are unusually brilliant, as in some febrile disorders, and the sclerotic appears bluish. In fact, fever is not infrequently observed in these cases. The menstrual flow is usually scanty and sometimes suppressed, but in a large proportion of cases, there is metrorrhagia or dysmenorrhœa. The urine is of low specific gravity and deficient in urea, and is generally very pale. Œdema of the face and ankles occurs in advanced cases. In a small proportion of cases there is a tendency to thrombosis, especially of the veins of the legs, which exposes the patient to a dangerous complication: pulmonary thrombosis. The cerebral sinuses may also be affected.

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* *Author's conclusion.*

** *Author's definition.*

[33] G. L. Gulland: Brit. Med. Jour., Jan. 12, 1907.

Birch-Hirschfeld[29] and Kockel,[30] according to Lazarus,[31] "believe that chlorotic blood has a greater tendency to coagulate, and they associate this with the increased number of blood-platelets." Indeed, we have seen that adrenoxidase is the fibrin ferment, and that the platelets are but droplets of the former. Stengel[32] refers to Leichtenstern's[33] study of 1658 cases of chlorosis in which thrombosis positively occurred only 11 times, and "probably in a mild form in a few other instances." Thrombosis is evidently a rare complication.

In typical cases of chlorosis, the red corpuscles are not diminished to any material degree, the salient feature being a reduction of the hæmoglobin. So decided is this in most cases, that the blood and the corpuscles themselves appear quite pale.

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[29] Birch-Hirschfeld: Congr. f. innere Med., Bd. xi, S. 28, 1892.

[30] Kockel: Deut. Archiv f. klin. Med., Bd. lii, S. 557, 1894.

[31] Lazarus: Nothnagel's "Encyclo. of Pract. Med.," vol. on Dis. of the Blood, p. 402, 1905.

[32] Stengel: *Ibid.*

[33] Leichtenstern: Münch. med. Woch., Bd. xlvi, S. 1603, 1899.

The percentage of corpuscles per cubic millimeter may exceed 80 per cent. of the normal, while that of the hæmoglobin may be 40 or lower. Properly speaking, however, what is absent is not hæmoglobin-proper, but that portion of it which remains in the red corpuscles, *i.e.*, hæmatin,* the true blood-pigment. Its albuminous portion, adrenoxidase, is not only present in a free state in the plasma,* but in rare instances it occurs in excess in the latter, as shown by the blood's increased coagulability—adrenoxidase being the fibrin ferment.* The paucity of hæmatin in the corpuscles renders them incapable of holding the albuminous portion of hæmoglobin,* they appear not only paler than normal, as stated, but smaller. Conversely, some may, here and there, appear enlarged, their undivided content in hæmatin being in that case sufficient to anchor an unusual quantity of adrenoxidase, owing to the abnormal quantity available in the plasma.* Small nucleated red corpuscles (normoblasts), which are derived from the bone-marrow, are also found in the blood, especially when an active regenerative process is going on. This proves futile, however, if hæmatin, the link between the red corpuscles and the albuminous hæmoglobin, be deficient.* The white corpuscles appear normal in all respects.

The marked diminution of hæmoglobin as compared to that of red corpuscles was first observed by Duncan nearly forty years ago, and the diagnostic importance has been sustained by the researches of Hayem, Sörensen, Stockman,[34] Gräber[35] and others. In 63 consecutive cases examined by Thayer in Osler's clinic,[36] the average of red corpuscles was 4,096,544, or over 80 per cent., while the average percentage of hæmoglobin was 42.3 per cent. The variations in size of the red corpuscles have remained unexplained; this is readily accounted for by the fact that the albuminous portion of the hæmoglobin has never been taken into account. As to the nucleated cells, Lazarus refers to the investigations of Neumann, Bizzozero and Ehrlich as having shown beyond a doubt, that they are "the evidence of active regenerative processes in the blood-forming organs (bone-marrow)."

Etiology and Pathogenesis.—Although the chromatin of meat, vegetables, fruit, etc., is the mother-substance of hæmatin, the proportion of metallic iron absorbed daily from these foodstuffs is at best very limited, namely, from 6 to 10 milligrams ($^1/_{10}$ to $^1/_6$ gr.) Moreover, this intake cannot be considered as an asset, since it varies but little, if at all, from the output by the urine and fæces. This indicates that the body absorbs from the alimentary proteids only just enough iron to replace the quantity normally utilized in the blood and tissues, and that in case of need, it draws upon its reserves in the liver, spleen, bone-marrow, etc.*

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* *Author's conclusion.*

[34] Stockman: Brit. Med. Jour., Dec. 14, 1895.

[35] Gräber: Cited by Lazarus: *Loc. cit.*

[36] Osler: *Loc. cit.*, p. 722, 1905.

We have seen in the article on iron that Bunge and Macallum had shown that the chromatin of the various proteids, animal and vegetable, was the mother-substance of hæmoglobin. As to the ingestion of iron, Stockman[37] found that "the quantity of metallic iron in ordinary dietaries seldom exceeded 10 milligrams (1/6 gr.) per day, and" that it "might be as low as 6 milligrams (1/10 gr.) in people of ordinary appetite and digestion." In a subsequent article, Stockman and Greig[38] demonstrated that "the iron metabolism is extremely small so far as intake and output is concerned." In one observation they "almost exactly coincided;" in others the output even exceeded the intake.

That conversely, iron may be lost or eliminated by way of the intestine, is sustained by considerable evidence. As far back as 1852 Bidder and Schmidt[39] ascertained that from six to eight times more iron was eliminated with the fæces, even during fasting, than with the urine. Gottlieb,[40] after feeding puppies on iron-free food, injected iron subcutaneously and found nearly 97 per cent. in the fæces. That this is by no means all excreted by way of the liver and with the bile, is proven by the experiments of Nathan,[41] which showed that the greater part of the iron excreted was carried to the large intestine by leucocytes. Hochhaus and Quincke[42] hold that the accumulation of iron in the submucous tissue of the large intestine is connected with its excretion, and that this is probably effected by the extrusion of iron-laden leucocytes. The opportunities for an output even in excess of the intake are evident.

In the great majority of cases of chlorosis, the disease is due to three morbid factors acting concurrently: (1) a deficiency of iron in the patient's regular diet, (2) depressed functional activity of the adrenal center,* and (3) its results,* imperfect digestion and assimilation.

As to the first cause, chlorosis is most common among ill-fed working girls or "sweat-shop" hands, whose diet seldom includes meat, fruit, and other foods rich in iron. Among the well-fed classes, chlorotics are likewise seen, but here the tastes are catered to, and the diet consists mainly of desserts, especially sweets, cakes, candy, ice-cream, milk, etc., all of which are extremely poor in, or devoid of, iron.

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* *Author's conclusion.*

[37] Stockman: Jour. of Physiol., vol. xviii, p. 484, 1895.

[38] Stockman and Greig: *Ibid.*, vol. xxi, p. 55, 1897.

[39] Bidder and Schmidt: "Die Verdauungssäfte u. d. Stoffwechsel," S. 411, 1852.

[40] Gottlieb: Zeit. f. physiol. Chemie, Bd. xv, H. 5, 1891.

[41] Nathan: Deut. med. Woch., Feb. 15 and 22, 1900.

[42] Hochhaus and Quincke: Arch. f. exp. Path. u. Pharm., Bd. xxxvii, S. 159, 1896.

Still, a multitude of girls, under identical conditions, do not suffer from chlorosis; a predisposing cause must prevail, therefore, in addition to these conditions. This is represented by the second cause mentioned. The age at which chlorosis most usually occurs, between 15 and 20 years, coincides with the period of greatest development, and when the adrenal system, therefore, is under the greatest stress.[*] If, as is often the case with the genitalia, the pelvis and the breasts in these cases, the organs forming the adrenal system are inadequately developed, they fail to meet the needs of the organism, and the vital process in all tissues is deficient.[*] Hence the muscular relaxation—the cause, in turn, of the weakness and lassitude, of the gastroptosis and enteroptosis, of the cardiac and vascular dilation, of the large and soft pulse, of constipation, of all menstrual disorders, etc., briefly, of all disorders in organs supplied with muscular elements. Hence, also, the many other morbid phenomena which general vascular relaxation entails, viz., accumulation of blood in great mesenteric channels, and recession of blood from the brain, lungs and skin, which, in turn, give rise to the familiar vertigo and tendency to fainting, dyspnœa, coldness of the surface and extremities, and pallor.[*] Finally, the hæmatopoietic organs themselves are the seat of inadequate metabolism, as shown by the average reduction of about 20 per cent. of red corpuscles, a proportion which is sometimes greatly exceeded.

The third cause is a normal consequence of the second. The dilation of the stomach and intestines, the constipation, and the many symptoms appertaining thereto, clearly point to imperfect digestion, a condition which in itself diminishes the likelihood that the small proportion of iron absorbed daily from the alimentary canal under normal conditions will be reduced. The intake being diminished, the reserves in the liver, spleen, etc., are drawn upon and the time finally comes when they are exhausted. This marks the onset of the disease, *i.e.*, the time when the red corpuscles, failing in their supply of hæmatin, gradually lose their hold upon what proportion of albuminous hæmoglobin, or adrenoxidase, the adrenal system is able to produce.[*]

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[*] *Author's conclusion.*

A diet deficient in iron thus becomes more of an aggravating factor than a primary cause of chlorosis; but we must not forget that in many instances the deprivation of wholesome food has existed from infancy, and that this in itself has tended to inhibit the development of the adrenal system, to prepare the soil, in other words, for chlorosis.*

All this applies as well to other causes of chlorosis. The great majority of cases occur in delicate, blond (*i.e.*, hair devoid of iron), illy-developed girls, and sometimes boys; while its causes are all of a debilitating kind, squalor, overwork, prolonged lactation, exhausting drains, profuse menstruation, masturbation, grief, nostalgia, etc., all of which tend to depress the functional efficiency of the adrenal center, directly or indirectly. This is the underlying cause of chlorosis, but only when the intake of iron from the blood fails to compensate for the output.*

The presence of adrenoxidase in unusual quantities in the plasma previously referred to, does not mean that an excess of this body is produced; it only signifies that what proportion is unabsorbed by the red corpuscles as the albuminous moiety of hæmoglobin circulates in a free state in the blood-stream. The activity of the adrenal center may, therefore, be far below normal and adrenoxidase still occur in the plasma.

Treatment.—To administer iron to such cases without increasing the functional activity of the adrenal system is not judicious, since it tends to increase constipation, while being wasted through the alimentary canal. The first feature which requires attention is the state of the blood. We have seen that it has a marked tendency to coagulate, and that this has been ascribed to blood-platelets. As this points to a deficiency of blood-salts,* the use of *normal saline solution* is indicated. The best method in these cases is to give it in the form of a large, hot (110° F.—43.3° C.) enema every other night, and, if the case be severe, to administer it in small quantities either endovenously or hypodermically, three days in succession, then every other day. The only other indication at this time is the *diet* recommended for anæmia, which includes foods rich in iron and alkaline salts.

At the end of a week, the blood will have regained, at least to a certain extent, its normal osmotic properties, and, the vegetables aiding, its normal alkalescence. The *thyroid gland,* in small doses, 2 grains (0.13 gm.) during meals, should then be begun, to enhance, through the adrenal system, metabolism in all its tissues, including the muscles of the heart and vessels.* The tone of the latter being improved, the distribution is equalized, and the adrenoxidase-laden plasma, instead of circulating in the larger, deeper vessels, where it is of but little use to the vital process of the organism at large, will now increasingly flow through the capillaries of all organs. As this applies also to the muscles of the stomach and intestine, the gastroptosis and the constipation will also be corrected. The resumption by the vessels of their normal caliber will have another all-important effect in this connection: it will correct the main factor in the loss of iron ingested, viz., *abnormal intrahepatic vasodilation and failure of the iron-laden leucocytes to circulate through the capillaries of the hepatic cells.* The iron, which, under these conditions, was imperfectly prepared for absorption, will then simply be excreted with the fæces—along with other food-products for the formation of hæmatin. After two weeks of thyroid gland, this stage will have been reached, and *iron,* preferably Blaud's pills, will now prove beneficial, since the stomach, liver and intestines will have been rendered able to prepare it for its assimilation by the red corpuscles, which, under the influence of the thyroid gland, will also have appeared in greater number in the blood.* *Adrenal gland* in 2-grain (0.07 gm.) doses hastens recovery by supplying the oxidizing constituent of the hæmoglobin.

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* *Author's conclusion.*

Others have observed the beneficial effects of thyroid gland. Battey Shaw[illegible] writes: "Capitan and Camus describe the favorable results of thyroid treatment in cases of severe chlorosis. Treatment by iron was found to be more successful when combined with thyroid treatment."

Other agents which have proven beneficial are the iodides. But even the *iodides* tend to increase the gastric disturbance in these cases. The syrup of the *iodide of iron* is sometimes borne without trouble, in 10- or 15-drop doses in a half tumblerful of water. *Strychnine,* in full doses, with inhalations of *oxygen,* is very efficient in mild cases. All are adrenal stimulants. The seashore hastens recovery in such cases.

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* *Author's conclusion.*

[illegible] Battey Shaw: "Organotherapy," p. 90, 1905.

HÆMOPHILIA.

Synonyms.—*Bleeder's Disease; Sporadic Hæmophilia.*

Definition.—A tendency to serious and sometimes uncontrollable hæmorrhage, due to a deficiency of fibrin ferment (adrenoxidase) in the blood and a corresponding diminution of the coagulability of the latter.*

Symptoms and Pathology.—The abnormal tendency to bleed is usually discovered through occurrences to which, as a rule, little importance is attached: nose-bleed, the extraction of a tooth, the application of a leech, a slight cut, vaccination, religious circumcision, etc. It may occur as the unsuspected source of metrorrhagia, or as the so-called "renal" hæmophilia, the urine being bloody. The skin is frequently the seat of hæmophilia; vesicles are formed either during apparent health or during eruptive diseases, scarlatina, varicella, etc., or more or less extensive extravasations appear under the skin, owing to capillary oozing, either as the result of a pinch, a blow, etc., or without provocation. The hæmorrhages may be internal; hæmophilia may thus act as the underlying cause of cerebral hæmorrhage. Reddish striæ of minute dilated vessels are sometimes witnessed in these cases.

The pathological anatomy of the disease affords but little information. The walls of the blood-vessels are said to be "thin" or "fatty," but Nancrede[44] says that this supposed thinness has only been witnessed once histologically. As to their being fatty, we have seen that "fatty degeneration" so-called is due to post-mortem changes. Abderhalden[45] recently ascribed hæmophilia to localized changes in the development and structure of the venules and arterioles of the regions involved, but, as shown below, vascular changes are of secondary importance in that they only tend to predispose these regions to act as outlets for the blood. In a case noted by Chauffard,[46] for instance, the recurrent hæmorrhages were always from the same areas.

Affections of the joints are very important in this connection, as many hæmophilics have lost their lives through surgical intervention. A joint in such subjects may suddenly and without appreciable injury become filled with blood, swell, become painful, etc., and slowly recover. This may recur repeatedly, but ultimately be attended by alterations of the synovial membrane and cartilages and finally deformity. It is in these cases of hæmophilic arthritis that a fatal error in diagnosis may be made. These cases usually show a pallor of the membranes; but the characteristic features are a history of hæmophilia, ecchymotic patches, and dilated capillaries. Recurrent epistaxis should always awaken suspicion. In tuberculous arthritis—the diagnosis usually made—the doughy patches of ecchymosis are absent, scars are likely to be present; inequality of the femoral condyles or of the head of the tibia may at times be discerned.

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* *Author's definition.*

[44] Nancrede: Dennis's "System of Surgery," 1895-96.

[45] Abderhalden: Ziegler's Beiträge, Bd. xxxv, S. 213, 1903.

[46] Chauffard: Le bull. méd., vol. x, p. 356, 1896.

Froelich,[47] who lays stress on these diagnostic points, states that aspiration of the joint, tenotomy and forcible extension should not be attempted in such cases. As shown below, however, even major operations may be done after appropriate treatment. Without such, however, surgical procedures of any kind, even cauterizations, as shown by Nové-Josserand,[48] are likely to lead to a fatal issue.

Etiology and Pathogenesis.—Heredity is a marked feature of hæmophilia, having been traced back in one family through nearly three centuries. It is often transmited by women not themselves affected (Nasse's so-called law). Another peculiarity is the marked fertility of bleeders' families. Again, a woman belonging to a family of bleeders may not herself be a bleeder, and may bear offspring who are, especially if her children are males.

The genealogy of a family of bleeders traced back nearly 300 years was recorded by Hoessli.[49] A marked example of transmission through non-hæmophilic women reaching back 200 years and affecting only males was published by C. Hicks.[50] All suffered from arthritic disorders. Steiner[51] observed a case in a negro, the first on record in this race, and traced it back to the great-great-grandmother. The family was extremely fertile, but both males and females were bleeders, though invariably transmitted through the females. Pincus[52] states positively that hæmophilics should not marry, but this view is subject to modification, in view of the facts submitted below.

Deficiency of the fibrin ferment—the adrenoxidase—in the blood is the underlying cause of hæmophilia. Fibrin ferment being a necessary constituent to the formation of fibrin, this substance is not formed in adequate quantities and the blood cannot coagulate.*

Hæmophilic subjects appear normal because coagulation requires an excess of fibrin ferment (adrenoxidase) over and above the needs of tissue respiration, and this excess is not available in them. As adrenoxidase is the oxygen-laden adrenal secretion, the primary cause, therefore, is a deficiency of adrenal secretion.*

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* *Author's conclusion.*

[47] Froelich: Revue d'orthopédie, vol. xv, p. 289, 1904.

[48] Nové-Josserand: Revue de chir., vol. xx, p. 768, 1899.

[49] Hoessli: Zeit. f. klin. Med., Bd. xv, S. 277, 1888.

[50] C. Hicks: Trans. Med. Assoc., Georgia, 1902.

[51] Steiner: Johns Hopkins Hosp. Bull., Feb., 1900.

[52] Pincus: Central. f. Gynæk., Bd. xxvi, S. 573, 1902.

I have shown that fibrin contains adrenoxidase and that it is identical with fibrin-ferment. That the adrenals are the source of this substance, and that a deficiency of their secretion is the primary cause of hæmophilia, is illustrated by the fact that stimulation of the adrenal center by its normal stimulant, *i.e.*, thyroid extract, counteracts the hæmophilia. This is emphasized by several cases given in outline under Treatment. In the first series, thyroid extract was employed empirically; in the second, Dr. W. J. Taylor's cases, I had recommended its use with the view of increasing the fibrin-ferment. Dr. Taylor carefully noted the blood's coagulability and found that it increased from day to day under the influence of the thyroid extract. Direct proof is afforded by the fact that adrenalin likewise arrests the bleeding in these cases; here it does simply what, as I have shown, it does in the lungs.

Treatment.—We have in *thyroid gland* not only a prophylactic, but also a curative agent, since it stimulates powerfully the pituitary body and raises its functional activity when its use is prolonged. Three grains (0.2 gm.) three times daily, *i.e.*, after each meal, suffice for this purpose. This causes gradual increase in the coagulating power of the blood, thus rendering even serious operations safe when the coagulating time has been reduced to the minimum normal, *i.e.*, three minutes.

The cases in which thyroid extract has been used successfully are already quite numerous. Délace[53] promptly stopped a menorrhagia which had lasted fourteen days in a hæmophilic; alveolar and subcutaneous hæmorrhages were also present. Instances in which unmistakable cases were successfully treated have been reported by Combemale,[54] C. R. Jones,[55] Scheffler,[56] E. Fuller[57] and others. The remedy was administered empirically in these cases, as previously stated. Not so with three cases reported by William J. Taylor,[58] however. Having in mind my view that it was by increasing the coagulating power of the blood that thyroid extract prevented hæmorrhage, he tested the blood's coagulating time: in a profuse bleeder requiring an operation it was reduced from 11½ minutes to 2 minutes and 6 seconds, and *nephropexy* was successfully performed, the wound being "remarkably dry." Thyroid gland was also given by him in a case of osteomyelitis attended with constant bleeding, and caused the latter to cease in one week. In a third case, it rendered possible the extraction of a tooth in a hæmophilic, no hæmorrhage occurring, though the gums were badly lacerated.

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* *Author's conclusion.*

[53] Délace: Jour. de méd. de Paris, vol. x. p. 46, 1896.

[54] Combemale: La méd. moderne. vol. ix, p. 278, 1896.

[55] C. R. Jones: Brit. Med. Jour., Nov. 10, 1900.

[56] Scheffler: Arch. de méd. et de pharm. milit., vol. xxxvii, p. 246, 1901.

[57] E. Fuller: Medical News, Feb. 28, 1903.

[58] W. J. Taylor: Monthly Cyclo. of Pract. Med., July, 1905.

Calcium chloride has likewise given good results, owing to the well-known influence on coagulation, but its effect is only temporary. It is given in 10-grain (0.6 gm.) doses, three times daily. If given to prevent bleeding during a minor operation (it allows of no other than trifling ones, extraction of teeth, opening of small abscesses, etc.), the coagulation time should be taken, and if this does not reach below five minutes, thyroid extract should be given in addition. *Digitalin* in full therapeutic doses is also useful.

Sympson,[59] Wallace,[60] Parry[61] and others have obtained good results with calcium chloride in hæmophilia. Ballantyne[62] used it successfully as an antenatal remedy, *i.e.*, to prevent hæmophilia in the third child of a woman whose two first children were bleeders. I used tincture of digitalis and obtained a prompt recovery in the case of a boy whom recurrent hæmorrhages had almost exsanguinated.

The most valuable local hæmostatic is *adrenal chloride* (1 to 1000 solution), gauze saturated with it being applied directly to the wound. A thick layer of the powdered extract also arrests the bleeding promptly. The ordinary styptics, *perchloride of iron, ergot,* etc., have been used, but seldom with success in serious cases. *Fresh entire blood* may be transfused, a small quantity being sometimes sufficient to arrest a profuse flow.

Adrenalin has been used successfully in the above manner by W. Milligan,[63] E. Francis,[64] and the extract by W. T. Thomas[65] and others. The use of entire blood was recommended by Hayem,[66] who thought that his "hæmotoblasts" caused the formation of a clot. I have shown[67] that these hæmatoblasts or blood-platelets are droplets of adrenoxidase, *i.e.*, of fibrin-ferment.

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[59] Sympson: Lancet, May 13, 1899.
[60] Wallace: Brit. Med. Jour., May 10, 1902.
[61] Parry: Lancet, Feb. 21, 1903.
[62] Ballantyne: Jour. Amer. Med. Assoc., Aug. 24, 1901.
[63] W. Milligan: Brit. Med. Jour., Feb. 1, 1902.
[64] E. Francis: *Ibid.*, May 28, 1904.
[65] W. T. Thomas: *Ibid.*, Nov. 23, 1901.
[66] Hayem: Le bull. méd., vol. ii, p. 1235, 1267, 1888.
[67] *Cf.* this vol., p. 829.

CHAPTER XXXII.

THE INTERNAL SECRETIONS IN THEIR RELATIONS TO PATHOGENESIS AND THERAPEUTICS (*Continued*).

THE ADRENAL SYSTEM IN INFECTIONS OF THE LYMPHATIC SYSTEM.

We have already seen that in tuberculosis, infection occurs to a great extent through the lymphatic system. In the diseases reviewed in the present chapter, syphilis and bubonic plague, infection not only occurs by way of this system, but the lymphatic glands act as foci for the development of pathogenic organisms. Hence the occurrence of buboes and kindred complications. An important feature emphasized is the need of energetic measures, as represented by the value of mercury, the iodides, etc., in the treatment of such disorders. Toxæmias are readily antagonized by ordinary adrenal stimulants because it is in the blood that the bactericidal and antitoxic agents which these remedies evoke first appear. In the lymphatic system, however, the protective process is relatively deficient, owing to the absence of red corpuscles, and therefore of adrenoxidase, in the lymph, a fact which involves a deficiency of auto-antitoxin in this fluid. Hence the freedom with which bacteria multiply therein; hence also the presence in the lymphatic glands of a multitude of phagocytes, small and large, whose purpose is to rid them of pathogenic elements of all kinds. The aim, therefore, should be to increase the proteolytic power and the aggressiveness of the phagocytes by agents which cause their digestive vacuoles to be well supplied with auto-antitoxin (their digestive triad) and to sensitize actively the bacteria. These requirements are met by mercury, the iodides and thyroid extract, as suggested below.

SYPHILIS.

Synonyms.—*Lues; Pox; Lues Venerea.*

Definition.—A specific disease due to inoculation, probably by the *spirochæta pallida*, characterized by three stages: (1) the *primary* stage, in which the seat of inoculation is converted into a specific ulcer, the chancre, whence the pathogenic organism may invade the lymphatic system if the body's autoprotective functions as exercised through the lymphatic phagocytes are unable to prevent it; (2) the *secondary* stage, or stage of general infection, during which the toxins or endotoxins of the specific germ excite a general reaction of the adrenal system and eruptions of various kinds; and (3) the *tertiary* stage, or period of sequelæ, provoked by the pathogenic organism or its toxins or endotoxins in various tissues during the secondary stage, characterized by a specific lesion, the gumma, and by marked debility or quasi-paresis of the adrenal system, which may be transmitted to offspring. *Congenital syphilis* is the expression, therefore, of inherited inadequacy or quasi-paresis of the adrenal system.**

Symptoms.—The *initial* lesion or "primary syphilis" occurs, as a rule, from two to three weeks after infection. Beginning as a small papule or abraded spot, it gradually develops into the chancre, which softens in the center, constituting an ulcer surrounded by a hard ridge—the "hard" or "indurated" chancre. This ultimately breaks down, leaving a scar. The appearance of the initial lesion is soon followed by enlargement of the adjacent lymph glands, forming the bubo or buboes. All these lesions are the seat of an active defensive process.

After a period varying from a few days to two weeks, the *second* stage appears. This is evidently due to a general reaction,* for it is attended with fever ranging from about 100° F. (37.8° C.) to as high as 105° F. (40.5° C.), characterized by irregular exacerbations and often by headache and insomnia. When the febrile process is high, hæmolysis may occur, as shown by the anæmic appearance of the patient. Cutaneous lesions of various kinds, none of which cause pruritis, are peculiar to this stage, viz., roseolar, squamous, papular, and even pustular, the pustules recalling those of variola and other eruptions, some of which often leave copper-colored pigmented patches. Syphilitic warts, which usually conjoin to form condylomata, may appear at the mucocutaneous junctions, while the mucous membranes of the tongue, nose, vulva, etc., often show similar lesions, *i.e.*, grayish, somewhat raised erosions: mucous patches. The second stage is a very active one—so active, indeed, that all organs, including the bones, the liver, the kidneys, the eyes, the ears, the hair, the nails, etc., may become the seat of inflammatory processes, *i.e.*, of local defensive reactions.*

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* *Author's conclusion.*
** *Author's definition.*

This stage—a period in which the infectious principle is fought at every step wherever met*—usually lasts from one year to eighteen months, when the disease either disappears—vanquished by the body's auto-protective resources*—or proceeds on its fell way, *i.e.*, to "tertiary syphilis," the third stage.

The *third stage* has been very appropriately defined as the "stage of sequelæ." Owing to the vascular lesions that are started during the second stage* and the formation in various structures of gummatous growths, morbid phenomena may appear in any organ through local pressure, distortion, denutrition and pressure-absorption. In the *respiratory tract*, for example, there may occur necrosis of the nasal cartilages and bones, causing the saddle-nose, perforation of the soft palate, and cicatricial adhesion of the latter to the pharynx; ulceration and gummata of the larynx and epiglottis, causing hoarseness, aphonia, cough, etc. The *lungs* may also be involved, especially in children. In the *brain*, pressure of gummata is a frequent source of paralysis, facial, ocular, etc. Syphilis is also a recognized cause of general paralysis.* Areas of softening in the brain itself, or its vessels, with formation of miliary aneurisms leading to hæmorrhages, may occur; symptoms of brain tumor may also appear. The pressure may be such as to cause passive congestion of the brain and the pia; violent headache, excitement, even epileptic convulsions, sometimes of the Jacksonian type, may be caused. In the *spinal cord*, symptoms of myelitis or of tumor, paralysis, such as hemiplegia, paraplegia and monoplegia, and locomotor ataxia, are relatively frequent results of spinal lesions. In the testicles the gummata may form hard, painless masses; suppurative orchitis may also occur and be followed by atrophy. Corresponding disorders of the ovaries may occur and provoke miscarriage. The *liver* may be the seat of gummatous enlarge-ments and later show areas of cirrhosis or fibrous cicatrices; ascites and jaundice may also be caused. The *cardio-vascular system* is not exempt; endocarditis, arteriosclerosis, gummata of the adventitia, etc., being not infrequently observed. On the whole, all tissues are exposed to the ravages of this terrible disease, each organ attacked giving rise to symptoms denoting perversion or arrest of its functions.

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* *Author's conclusion.*

In *congenital syphilis,* symptoms may be present at birth, which usually develop later—roseola, excoriations at the mouth and anus (the latter appearing also as if scalded) readily developing into mucous patches and condylomata. An eruption of ulcerative bullæ around the wrists, pemphigus neonatorum, a typical sign of syphilis, is also frequently observed. The viscera, and particularly the liver, spleen and kidneys, are pre-eminently the seat of connective tissue lesions similar in every respect to those observed in the adult. Syphilitic rhinitis, the "snuffles," which obstructs the nasal cavities, and may be followed later by necrosis of the nasal cartilage, contributes greatly to the general wasting or marasmus, by interfering with oxygenation. The special senses, especially the eyes—interstitial keratitis being commonly observed—and ears are always threatened. The cerebro-spinal system, especially at birth, may be the seat of apoplectic effusions owing to lesions of the arteries. The osseous system and particularly the diaphyso-epiphyseal junction of long bones is often involved, the rosary at the costocartilaginous junctures observed in rickets and nodular thickenings on the tibia and other bones, being readily discernible in most instances. When the second dentition is reached, the permanent teeth appear notched, irregular and "pegged," the two upper incisors being particularly deformed in this manner, *i.e.,* the Hutchinson teeth.

This brief résumé of the symptomatology of syphilis contains but the most salient features, but it suffices to suggest that if from the beginning of the first or second stage of the disease, an active defensive process is in operation, it would, when raised to its highest efficiency by remedial measures, prevent the ravages which constitute the third stage.

Etiology and Pathogenesis.—The pathogenic organism of syphilis, found in the primary and secondary cutaneous and glandular lesions, and in some of the tertiary lesions, is probably Schaudinn and Hoffmann's recently discovered *spirochæta pal-*

lida, a slender, corkscrew-like spirillum. Inoculation experiments have given rise to typical ulcers containing this parasite; but it has not so far been possible to cultivate it in artificial media.

The initial lesion, the chancre, is from the start the seat of a defensive process. It is at once invaded by various phagocytic leucocytes, lymphocytes and epithelioid macrophages, which accumulate *in situ* along with connective-tissue and other cells connected with the process of repair.*

That the spirochæta pallida is the specific germ of syphilis is sustained by considerable evidence. It must not be forgotten, however, that Lustgarten's bacillus was also found in all lesions. That the initial sore is invaded at least by scavenger cells is now generally recognized. Thus, Ohlmacher[1] states that, "like other allied infections, syphilis seems to irritate principally the elements of the connective tissue, and in consequence we find in both *early* and late lesions, a proliferation of endothelioid cells, small round (lymphoid) cells, and giant cells. As in most other infections, the endothelioid cells, giant cells, and certain migrated leucocytes engage in phagocytic activity in the effort to rid the body of the noxious invaders or to remove the detritus of cellular necrosis." The defensive process is essentially local, however. Thus, Hallopeau[2] found that "the pathogenic action of the toxins is *nil* during the periods of incubation and latency of the disease," a fact which shows, from my viewpoint, that these toxins do not evoke a protective reaction from the start. I regard this as a very important fact from the standpoint of prophylaxis, for such being the case, the immediate use of remedies such as thyroid, iodine, etc., which powerfully stimulate the thyro-adrenal functions must tend to prevent general infection even when the chancre is feebly developed.

The germ-laden leucocytes, epithelioid cells and giant-cells—all phagocytes—are the "syphilized cells" of Besiadecki, Otis and others, which become infectious through the fact that either as micro- or macrophages, they ingest the specific organism.* In some cases they succeed in preventing infection. If, however, the vital functions of the patient be at all depraved, either through alcoholism, antecedent disease, starvation, etc., the production of adrenoxidase, trypsin, nucleo-proteid and thyroidase, the constituents of auto-antitoxin, be deficient, these defensive cells, inadequately supplied with this bacteriolytic substance, fail to destroy the germs.* On leaving the seat of infection to enter the lymphatic vessels, therefore, they are laden with these pathogenic organisms and infect the lymphatic glands of the groin, giving rise to the "buboes," and finally infect the body at large.

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* *Author's conclusion.*

[1] Ohlmacher: "Amer. T. B. of Physiol.," p. 259, 1901.

[2] Hallopeau: Annales de dermat., 4 série, vol. v, p. 736, 1904.

That, as I suggest, general infection is influenced by debility of the adrenal system's protective power, owing to general adynamia, and as manifested through the leucocytes, harmonizes with established facts. The debilitating influence of alcohol and squalor is well known. Thus Prof. Neumann[3] recently emphasized the fact that syphilis "is more common in ill-nourished persons and in hospital patients than in those seen in private practice" and that "alcohol diminishes the resistance of the tissues to specific infection." The "resistance of the tissues" means, in the light of the evidence I have adduced, a deficiency of auto-antitoxin in the blood and cells: Applying this principle to the prevailing conception, the rôle of the leucocytes, as I have depicted it, will suggest itself. G. Frank Lydston[4] in an able review of the whole subject, says, for instance: "The first effect of the syphilitic infection is a gradually increasing accumulation of leucocytes—*i.e.*, white blood-cells or lymph-cells—at the site of inoculation, produced by a modification of the normal leucocytes and connective tissue elements through the influence of the syphilitic infection." ......"The *previously normal* accumulated cells (the syphilized cells of Besiadecki, Otis, *et al.*) contain the germ of syphilitic infection. They become *larger*, more *granular* and contain numerous nuclei [giant cells] and possess exaggerated powers of proliferation and *amœboid movement*."..... "This much is certain, however, that just as the leucocyte is the primordial cell in the normal physiological processes of growth, so is it the basis of all so-called pathological processes, and particularly those of syphilis, when modified in the manner peculiar to the particular disease."

Interpreted from my standpoint, however, the normal phagocytic leucocyte is fully able to digest the pathogenic germs and to convert them into granulations that are more or less useful to the body at large, while the leucocyte, deficient in bacteriolytic bodies and moving in blood deficient in thyroidase (opsonin), is not, and acts as infecting agent.

Some of the germ-laden leucocytes carried along by the torpid lymphatic current, finally reach the receptaculum chyli, along with quantities of specific germs produced through multiplication in the lymph and lymphatic glands, and are finally emptied into the blood-stream. When the germs and their toxins have accumulated sufficiently in the blood, the *second stage* begins; which means a reaction of the body to protect itself, through the adrenal system, against infection.*

The "syphilitic fever," marked in proportion as the reaction is severe, is accompanied by a marked rise of the blood-pressure due, as in arteriosclerosis, to hypermetabolism in the vessel-walls. So marked is the vascular tension that the blood is driven by the deeper vessels into the peripheral capillaries, which become intensely congested. As the specific germs and their toxins, waste-products of the prevailing hypermetabolism (including various acids), detritus, broken-down cells, etc., are inadequately removed from the cutaneous capillaries, owing to the torpor of the blood-stream in the vessels,* many kinds of eruption may appear, one of which, the syphilitic roseola, usually leaves copper-colored spots.

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* *Author's conclusion.*

[3] Neumann: Wiener klin. Woch., Bd. xvii, S. 551, 1904.

[4] Lydston: Sajous's "Analyt. Cyclo. of Pract. Med.," Art. on Syphilis, vol. vi, 1898.

The fever, which, we have seen, may attain 105° F. (40.5° C.), is of course, as elsewhere, due to excitation of the test-organ and adrenal center—or thermogenic center—by the poison. So marked is the excess of auto-antitoxin in the blood, in fact, that a slight increase of this protective compound suffices to produce hæmolysis. This explains the phenomenon known as "Justus's test" in which one large dose of mercury is sufficient to produce a sharp hæmolysis. This destruction of red corpuscles (10 to 15 per cent.), according to Justus,[5] "is a specific phenomenon, and is not observed in the blood of healthy persons." This is accounted for from my standpoint by the fact that the mercury, by suddenly exciting the test-organ, increases the proportion of auto-antitoxin in the blood sufficiently—in addition to the excess already present in the latter—to render it hæmolytic. All this proves that an intense protective process is going on in the blood.

The capillary hyperæmia is well shown by the leucoderma. That it is at least closely related with the second stage is suggested by Fivelsky's[6] statement that "these pigmentations may remain for several years and can be regarded as among the best signs of the secondary period"—though as observed by Lewin,[7] it is also met with in subjects who have never had syphilis. It has been ascribed by some writers to "a transient congestion of adrenals," according to Frattalli.[8] This conclusion is warranted—since, as we have seen, the adrenal system is overactive—but only in the sense that the blood is thus caused to contain an excess of the adrenal active principle which, as I have shown in the thirteenth chapter, is the main factor, when oxidized, in bronzing and kindred pigmentations.

The relationship between this cutaneous hyperæmia and the eruptions of all kinds observed during the second stage is generally recognized. Thus, Lydston[9] states that "the syphilitic roseola is due to dilation of the cutaneous capillaries and subsequent stasis, and the exudation of leucocytes [which, we have seen, contain the germs] and red corpuscles into the implicated integumentary area." L. S. Schmitt,[10] referring to the fact that Veillon and Girard[11] "found the spirochæta pallida in sections of syphilitic roseolæ of four days' duration" and that "the sections showed intense capillary and beginning perivascular infiltration," states that "the *organisms* were found in the *terminal* subpapillary capillaries and in some of the subpapillary vessels" and that "a few were found in the perivascular nodules." Schmitt concludes from this "that the roseolæ are not of toxic origin, that they are due to a true parasitic embolus lodged in the terminal capillaries of the skin and producing a perivascular infiltration."

The *third stage*, as already stated, is not a manifestation of the syphilitic infection, but of a variety of disorders which occur as sequelæ of the lesions that the presence of the pathogenic organism in various organs has provoked, directly or indirectly, during the second stage.

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* *Author's conclusion.*

[5] Justus: Virchow's Archiv, Bd. cxl, S. 91, 1895.

[6] Fivelsky: Annales de dermat. et syph., 3 série, vol. ii, p. 418, 1891.

[7] Lewin: Charité Annalen, Bd. xviii, S. 614, 1893.

[8] Frattalli: Clinica dermosifil della R. Univ. di Roma, Oct., 1895.

[9] Lydston: *Loc. cit.*

[10] L. S. Schmitt: Cal. State Med. Jour., Mar., 1906.

[11] Veillon and Girard: C. r. de la Soc. de biol., vol. lix, p. 652, 1905.

The arterial lesions are in part due to a process similar to that which prevails in arteriosclerosis,* viz., to excessive metabolic activity in the vessel-walls, and particularly in those of the vasa vasorum.* These minute nutrient vessels becoming occluded, the areas they nourish become necrosed and, ultimately, fibrous and calcareous.* This morbid process is greatly aggravated by vascular lesions provoked by the presence of the germs, the reparative process which follows entailing likewise local sclerosis. Any or all vessels may thus be affected, the lesions being either of the inflammatory type: endo- or periarteritis, and endo- or periphlebitis; or secondary thereto: thickening or fibrosis of their walls, entailing partial or complete obstruction. Thrombosis may also occur.

The only lesion that may be considered as truly syphilitic is the gumma, a gelatinous mass varying greatly in size, and containing at first endothelioid and mononuclear cells (both phagocytic), then a cheesy mass. Their microscopical resemblance to tubercles is such as to indicate that they fulfill a rôle similar to that carried on by these masses in tuberculosis (*q.v.*) viz., to enclose colonies of pathogenic bacteria and cellular detritus* and thus arrest dissemination of the germs. They may become hard and dense, and are traversed by fibrous bands forming meshes which enclose their caseous contents, however, and being liable to form anywhere, particularly in the liver, testis, spleen and brain, and in the bones, which they may soften and destroy; they add a formidable pathogenic factor to the already formidable vascular lesions, through the pressure which they exert. They often break down, but this either leaves an open lesion or a mass of cicatricial tissue which is in itself a menace in certain regions, the central nervous system, for example.

That syphilitic infection is absent when the third stage is reached is shown by the absence of the pathogenic organism during this stage. Sobernheim and Tomasczewski,[12] for instance, having examined 58 cases of syphilis for the spirochæta, found it in all with the exception of the only 8 cases of tertiary syphilis. This fact, which has been confirmed by other observers, accounts for non-communicability of tertiary lesions.

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* *Author's conclusion.*

[12] Sobernheim and Tomasczewski: Münch. med. Woch., Bd. III, S. 1857, 1906.

This should not be considered as a law, however, for, as is well known, relapses of the disease may occur years, even decades, after apparent exhaustion of the infection, a fact ascribed by Virchow to retention in the lymph-nodes of the pathogenic agent.

The prevailing view is that the arteriosclerosis of syphilis is an independent process. Thus, Neumann[13] stated recently in one of his lectures that "arteriosclerosis *favors* tertiary lesions." As I show above, however, it can clearly be caused by syphilis, *i.e.*, through the prolonged hypermetabolism to which the vessel walls are submitted during the secondary period. This further emphasizes the need of curative measures as early as possible in the second stage. That lesions can be caused in the walls of vessels is emphasized by the fact that Buschke and Fischer[14] found the spirochæta pallida attached to the vascular endothelial cells and traced them into, and even through, the vessel walls.

A cardinal feature of the third stage is the depressed condition of the adrenal system.* Although lesions of the adrenals themselves are rarely observed in syphilis, they are sufficient in some instances to cause bronzing and other manifestations of Addison's disease. This bronzing is due to the exhausting stimulation to which the test-organ, and through it, the adreno-thyroid center, is submitted during the secondary period.*

That physical degeneration is a paramount factor of tertiary syphilis is generally acknowledged. The connection with the adrenal system is emphasized by the general adynamia and the pigmentation occasionally observed both in acquired and congenital syphilis and also by the fact that Addison's disease may develop as a result of syphilitic infection, as in cases reported by Sacaze,[15] Chauveau, and others. The adynamia can hardly be always ascribed to disease of the adrenals *per se*, for in a study of 100 autopsies of syphilitic children, Hecker[16] found the adrenals rarely involved, though Guleke[17] found the adrenals of three cases out of eight of *bona fide* inherited syphilis, the seat of necrotic foci. Engel-Reimers,[18] Fürst,[19] Wermann[20] and others have reported instances in which the thyroid was enlarged, thus indicating impairment of the functions of this organ. It is thus apparent that the two secreting structures of the adrenal system, the adrenals and thyroid, may, either directly or indirectly, be compromised by syphilitic infection.

The relationship of cancer to syphilis is very interesting in this connection. The prevailing view is that syphilitics are proof against cancer. Indeed, Roger Williams[21] in an examination of 165 breast-cancer patients, did not find undoubted signs of syphilis in a single instance, while in 160 uterine-cancer cases similarly examined, only one presented signs of having had syphilis. This is accounted for in some cases, from my standpoint, by the fact that during the secondary period, the blood is so rich in auto-antitoxin that the initial lesion of cancer is promptly counteracted, while during the tertiary period and the resulting adynamia, the blood is too poor in auto-antitoxin to sustain the process of cellular growth to which the tumor is due. Various recorded instances seem to have proved that cancer can be grafted on syphilis; but examined in the light of my views, their number is subject to reduction. Thus, A. Patterson[32] reported a case of scrotal epithelioma in which, notwithstanding repeated removal of neoplastic tissue, the wound refused to heal. On learning that the patient had been in the army, iodide of potassium was administered. The wound healed rapidly and the patient was still in good health when last seen, 10 years later. Now, this case is ascribed to syphilis, but inasmuch as I have shown that the iodides are also capable of stimulating the adrenal system and thus curing cancer, syphilis may be eliminated in Patterson's case—as it could in all cases in which the diagnosis of syphilis is based on the results of antisyphilitic treatment. On the other hand, there are many cases recorded in which cancer will develop upon syphilitic leucoplakia, syphilitic scars, etc.—a sufficient number, in fact, to indicate that the supposed protection afforded by syphilis (aside from the secondary stage) is a myth.

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* *Author's conclusion.*

[13] Neumann: *Loc. cit.*

[14] Buschke and Fischer: Berl. klin. Woch., Bd. xliii, S. 6, 1906.

[15] Sacaze: Gaz. des hôpitaux, vol. lxviii, p. 58, 1895.

[16] Hecker: Deut. Archiv f. klin. Med., Bd. lxi, S. 1, 1898.

[17] Guleke: Virchow's Archiv, Bd. clxxiii, S. 19, 1903.

[18] Engel-Reimers: Jahrsb. der Hamburgischen Stadtskrankenanstalten iii; Therap. Monatshefte, Bd. ix, S. 267, 1895.

[19] Fürst: Berl. klin. Woch., Bd. xxxv, S. 1016, 1898.

[20] Wermann: Berl. klin. Woch., Bd. xxxvii, S. 122, 1900.

[21] Roger Williams: Edinburgh Med. Jour., Oct., 1898.

Treatment.—Syphilis is essentially a disease in which the adrenal system can be utilized advantageously by the physician, since the local primary sore and the general infection it entails, the secondary reaction, and even the typical expression of the third stage, the gumma, and to a certain extent the vascular lesions, can be influenced through this system.[*] The manner in which *mercury* and the *iodides* produce their curative effects in this disease suggests itself in view of their powerful stimulating action on the test-organ, and through it on the adreno-thyroid center.[*] This applies as well to *thyroid extract,*[*] which not only increases the functional activity of the adrenal system, but also, by adding thyroiodase (opsonin) to the blood, sensitizes the germs for the phagocytes.[*]

In the first volume[33] I urged[*] "that simultaneous impairment of the functions of both the anterior and posterior pituitary bodies accounts for the ravages of syphilis," and that it was through this system that iodine and mercury produced their beneficial effects. Thyroid extract was used by Menzies[34] as an adjuvant to other methods and is recommended by him. Gouladsé[35] used it in a very severe case, in which the alæ nasi and one ear were destroyed by ulceration, besides marked adynamia and emaciation. The usual measures having failed, thyroid gland was tried. On the third day improvement began; the ulcers healed promptly, all morbid phenomena ultimately disappearing. Champlin[36] states that where other remedies fail "thyroid gland, 2 grains (0.13 gm.) three times daily with sodium bicarbonate, brings about results truly marvelous," his report being based on 20 cases.

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[*] *Author's conclusion.*
[32] A. Patterson: Scottish Med. and Surg. Jour., Aug., 1899.
[33] *Cf.* vol. i, p. 777.
[34] Menzies: Brit. Med. Jour., July 7, 1894.
[35] Gouladsé: Vratch, No. 30, p. 854, 1895.
[36] Champlin: Amer. Jour. Clin. Med., Apr., 1906.

During the *primary stage*, the use of *thyroid extract*, 3 grains (0.2 gm.) every three hours, the first day, then after meals, is indicated as a prophylactic to increase the opsonic properties of the blood and thereby render the pathogenic organism more vulnerable to the phagocytes.* Mercurials alone are not protective at this stage.

During the initial stage, the phagocytes are alone entrusted with the protection of the body. Although mercury excites the adreno-thyroid center, the thyroidase produced is inadequate to raise materially the sensitizing properties of the blood. Neisser,[27] in fact, found that injections of sublimate one hour after inoculation of the syphilitic virus did not prevent development of a chancre near the seat of inoculation nor general infection. Nor does washing with a solution of sublimate (1: 4000 or 5000) proposed by Guinard[28] protect, a fact ascertained by Roux and Metchnikoff.[29] I only suggest thyroid extract, owing to the physiological action I attribute to it; but I know of no instance in which it has been tried.

The *second stage* is essentially the stage for *mercury*, since this drug excites violently the test-organ and correspondingly increases the proportion of auto-antitoxin in the blood-stream.* The simultaneous use of *thyroid gland* is also indicated, however, to increase the vulnerability of the specific germs to the phagocytes, practically the only protective agents in the lymphatic system.*

The effect of mercury—of stimulation of the adrenal system, from my standpoint—on the *Spirochæta pallida* was shown recently by Freund.[30] As soon as the patients were given this remedy, these parasites gradually became less numerous, until, after a course of inunctions, they completely disappeared from the blood. Lydston[31] holds that "the slow, continuous and moderate use of mercury" . . . . . "without at any time producing its full physiological effects will generally bring about a cure that can be accomplished in no other way." This harmonizes perfectly with the interpretation I have offered of the action of mercury, viz., that salivation marks the beginning of *excessive* and *destructive mercurialism*.

The *third stage*, though not a direct manifestation of the infection, affords three morbid processes of far-reaching pathogenic influence which can be antagonized by adrenal stimulants,* particularly *thyroid gland* and the *iodides*. These are (1) the general adynamia, which is offset by the greatly augmented oxygenation and general nutrition; (2) the pressure symptoms

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* *Author's conclusion.*

[27] Neisser: Deut. med. Woch., Bd. xxxii, S. 52, 1906.

[28] Guinard: Annales de dermat. et syphil., 4 série, vol. ii, p. 1037, 1901.

[29] Roux and Metchnikoff: Cited by Metchnikoff: "The New Hygiene," p. 99, 96.

[30] Freund: Münch. med. Woch., Bd. iii, S. 1819, 1905.

[31] Lydston: *Loc. cit.*

(which may cause various forms of paralysis) due to gummata, absorption being enforced through the fact that these agents promote leucocytosis, and therefore phagocytosis—a process which applies likewise to the production of the proteolytic triad (auto-antitoxin) which breaks down these masses; and (3) the mechanical constriction of arteries to which denutrition and atrophy of many structures are due, by increasing the general pressure (lowered during the third stage) and thus causing a greater volume of blood to circulate in all capillaries, including those of the cerebro-spinal system, the neuroglia, the neuro-fibrils, the neurons themselves and their axis-cylinders, which are all adrenoxidase-laden plasma channels.*

That the conditions referred to are benefited by the iodides is so well known, that I deem it unnecessary to submit evidence.

During the second and third stages, the alkalinity of the blood is often greatly reduced, a fact which suffices to thwart the beneficial effects of the remedies used.* This lowered alkalinity is shown by a noticeable increase of blood-plates.* The use of *alkaline waters* and an increase of sodium chloride in the food,* all supplemented, if necessary, by large warm enemas of *saline solution,* aids the curative process materially by enhancing the osmotic and antitoxic power of the body fluids and facilitating the migration of leucocytes, including the phagocytes, where their aggressive, protective and reparative work is needed.*

Losdorfer, Vörner[32] and others have observed a large increase of blood-plates in the blood of syphilitics, irrespective of the stage. In the first volume[33] I pointed out that these blood-plates were droplets of adrenoxidase derived from the red corpuscles, which were visible only when the alkalinity of the blood was greatly reduced.

As to the use of normal saline solution, Heineck[34] states that it has been found valuable "in malignant forms of syphilis that fail to respond to the anti-syphilitic treatment." Gastou and Quinton[35] found that isotonic injections of sea-water added to the medicinal treatment greatly enhance the curative process.

Of course, the introduction of *salvarsan* on the scene has relegated all other methods of treatment to the rear.

CONGENITAL SYPHILIS.—In the definition I specified that the transmission of "syphilis" to offspring was in reality the transmission of a debilitated or quasi-paresis of the adrenal system. I would suggest, as an efficient agent in these cases, *thyroid gland.*

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* *Author's conclusion.*

[32] Vörner: Deut. med. Woch., Bd. xxviii, S. 897, 1902.

[33] *Cf.* vol. i, p. 715.

[34] Heineck: Surgical Clinic, Apr., 1912.

[35] Gastou and Quinton: Presse médicale, vol. xii, p. 453, 1905.

I append hereto the methods employed by T. W. Kilmer.[illegible] by mercurials and iodides. Both these agents being powerful stimulants of the adrenal system, the results obtained are readily accounted for. "Having employed the various forms of mercury in the treatment of congenital syphilis," writes Dr. Kilmer, "I have discarded practically all of them except the employment of *bichloride of mercury*, administered by the mouth. This has been, in my experience, the best method in which to use this drug. Ointment soils the clothing, and is soon discarded by the parents as being too dirty and troublesome. In using the bichloride of mercury I usually administer it in plain water to infants, or in some simple vehicle to older children. Each teaspoonful contains the desired dose of mercury. To an infant I begin by giving $^1/_{200}$ of a grain [0.00033 gm.] morning and night: to a child one to two years old, commence with $^1/_{100}$ of a grain, [0.00065 gm.] morning and night, keeping this up for a few days, and then give him the same dose three times a day; then, after a day or two increase the dose to $^1/_{100}$ of a grain [0.00065 gm.] to an infant of six months; or $^1/_{50}$ of a grain [0.0013 gm.] to a child one or two years old. If no symptoms of mecurialization are seen, which in infants occur in the form of loose, greenish stools, increase the dose slightly up to the abatement of the symptoms or the occurrence of loose, greenish stools. It is impossible to salivate an infant, and the physiological limit to the administration of mercury is manifested by the presence of loose, greenish stools in nearly every case.

"Infants bear the mercurials well. When the dose is reached which causes either a diminution of the symptoms of syphilis or loose, greenish stools, hold the patient at this dose until the symptoms of syphilis disappear.

"It is oftentimes of advantage in older children to combine *iodide of potash* in the form of the saturated solution, two or three drops three times a day up to a diminution of symptoms or the production of an iodide rash. It is best to give separate prescriptions for the mercury and for the iodide of potash. The iodide is generally well borne by young children.

"After the subsidence of all symptoms the child should be examined monthly for six months, and then every two months for a while, and then every six months until puberty. It is always necessary, to my mind, to give these syphilitic children a one to two weeks' course of antisyphilitic treatment out of every six months until adolescence is reached, and then caution them to be examined twice a year for the remainder of their life. It is quite an easy matter to cure a patient with syphilis, but to *keep him cured* is a far more difficult proposition! Aside from the medicinal antisyphilitic treatment, of course, a régime of proper diet and hygiene should be instituted."

PLAGUE.

SYNONYMS.—*Bubonic Plague; Black Death; Malignant Adenitis.*

Definition.—Plague—a virulent infectious disease characterized by the formation of buboes and the development in some

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[illegible] T. W. Kilmer: Monthly Cyclo. of Pract. Med., May, 1907.

cases of pneumonia—is due to the Kitasato-Yersin bacillus. On penetrating the lymphatic system, this germ multiplies therein, causing the characteristic lesion of the disease, the bubo, and secretes a toxin which tends to paralyze the sympathetic center in the pituitary body, and to inhibit the function it governs, general nutrition. It is to the resulting adynamia that the development of pneumonia is due, through the agency of the ever-present pneumococcus.*

I cannot do more in this connection, owing to want of space, than to submit the conclusions to which a study of the relationship between the ductless glands and bubonic plague has led me, reserving the evidence itself for another article to be published elsewhere. This section is only published here, in fact, for the benefit of those colleagues who are fighting this terrible disease in the East, and in the hope that the new ideas advanced as to treatment may be of some slight use to them.

Symptoms.—The true symptoms of the disease are usually preceded by a period of incubation varying from two days to a week, characterized by increasing weakness, and toward the end of the period by nausea and perhaps vomiting and vertigo. The acute stage is ushered in by rigors or a chill, the temperature rising somewhere between 101° and 105° F. (38.3° to 40.5° C.). The patient reels like a drunkard, owing to marked vertigo, and complains of violent headache and great lassitude. This sudden and early exhaustion is apparent in the features, the drooping eyelids, the apathetic air, and the evident indifference to surroundings constituting the *facies pestica* characteristic of the disease. The respiration is usually rapid, the pulse also; the conjunctivæ are congested, and keratitis, iritis, or panophthalmia is sometimes observed. The tongue is swollen, shows the impression of the teeth, and is covered with a whitish fur resembling mother-of-pearl (Bulard).

In the bubonic form, the bubo appears during the first hours of the malady and is usually unique. In the order of frequency, it presents itself in the groin, the axilla, or the neck. It develops with rapidity, and is well advanced as early as the beginning of the second day, and is always very sensitive to the touch almost from the start. The neighboring tissues are tumefied and œdematous, especially in the parotid region. When this locality is invaded, œdema of the larynx is to be feared.

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* *Author's definition.*

On the second day, the bubo is about the size of a pigeon's egg, and there is aggravation of all the constitutional symptoms, the pulse reaching sometimes 140. Delirium now appears and the stage of apathy is replaced by one of excitement, during which the patient may try to get up. Physical disorders become manifest, fixed ideas predominating. Functional disturbances of speech are also frequently observed. On the third day, all the symptoms become still further aggravated, the pulse reaching 140 or beyond, and the bubo attains perhaps the size of a hen's egg, and suppurates. Occasionally it becomes gangrenous. Carbuncles may develop in different parts of the organism. Extensive petechiæ are usual: the "plague-spots" of older writers. Hæmorrhages from mucous membranes, the nose, the lungs, etc., are frequently observed. In some epidemics hæmorrhages are witnessed in all cases, the buboes assuming an hæmorrhagic type.

Death, in the majority of fatal cases, generally occurs about the fourth day, either from toxic paralysis of the respiratory or cardiac centers or from collapse. If the first four or five days—the acute stage—are passed safely, the chances of recovery are favorable. On the other hand, a stage of marasmus or profound depression may appear on the fifth day and the patient succumb on the sixth. Much depends upon the condition of the heart. Some cases, especially in children, are very benign, showing but an insignificant rise in temperature, slight inguinal or axillary pain, general depression and ephemeral torpor. Such cases, however, are apt to occur early in the course of an epidemic. On the whole, the disease shows a very high rate of mortality.

In the pneumonic or septic variety there is profound septicæmia. The pulmonary inflammation closely resembles commencing influenza (Lewin) and does not show clear physical signs. It is a form of confluent lobar pneumonia without apparent or noticable implication of the lymphatic system. It begins also with a chill, severe pain in the side, and more or less severe cough with rusty expectoration. The plague bacillus is always found in the latter. In this variety death may occur within twenty-four hours.

Some epidemics exhibit symptoms representing both varieties.

Etiology and Pathogenesis.—The disease is due to a bacillus discovered by Kitasato, in 1894, and which is probably communicated to men through the bites of insects, fleas especially, themselves contaminated by the blood of contaminated animals, especially the rat. Filth and bodily neglect are predisposing causes. When the infection has occurred, the germ invades the lymphatic system and gives rise, as in syphilis, to buboes, the characteristic objective symptom of the disease.

The relationship of the disease with the ductless glands is shown by various phenomena which the presence of the buboes does not explain, viz., the toxæmia.* The combination of marked exhaustion and weakness at the commencement of the disease, the moist non-tremulous mother-of-pearl tongue of Bulard and the delirium and excitement on the second or third day, indicate the identity of the center affected, viz., the sympathetic center, and the character of the morbid process: intense depression or paresis of this center.* The tendency to capillary hæmorrhages in the viscera and subcutaneous tissues points from a different direction to the nature of the peripheral disorder: paresis of the arteries, a fact further shown by the impaired nutrition of the peripheral tissues and bones,* which in some cases may even undergo necrosis. The intense muscular weakness is a normal outcome of this condition and to it also is due the development of pneumonia,* owing to the ubiquitous presence in the respiratory channels of the pneumococcus and its readiness to multiply when the vital functions are torpid.

Fortunately, the test-organ is not influenced in the same way and soon reacts,* as shown by the rise of temperature, which may reach 105° F. (40.5° C.). In many cases, however, its reaction is inadequate* and the temperature does not exceed 101° F. (38.3° C.). Under these conditions the case, if at all a severe one, rapidly assumes a lethal trend, the body's defenses being unable to save it.*

Treatment.—The main indications, in the light of my views, are three in number. The first of these is to raise the functional activity of the adrenal system to its highest possible potential, to check the multiplication of the bacillus in the lymph and the blood.[*] As its toxin is very sensitive to heat, both pathogenic elements are thus antagonized.[*] *Mercury*, of all agents, does this most promptly and should be injected intravenously. The best agent for this purpose is the *biniodide*, $^{1}/_{6}$ to $^{1}/_{2}$-grain (0.01 to 0.03 gm.) dissolved in 15 minims (1 gm.) of water every four hours, until the first signs of mercurialism appear. It is painless when injected—preferably in the veins of the elbow. The test-organ being promptly stimulated, the blood is soon rendered richer in auto-antitoxin, and the phagocytes which penetrate into the lymph-channels and glands likewise.[*] This salt does not contain enough iodine to increase adequately the proportion of thyroidase (opsonin) and the bactericidal activity of the phagocytes.[*] *Sodium iodide*, 15 grains (1 gm.) in a large glass of water, should be given orally with each dose of mercury and continued every four hours after the use of the latter drug is stopped.

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* *Author's conclusion.*

Pending the action of these agents, *adrenalin chloride*, 1-1000 solution freely diluted, may be given hypodermically, remembering, however, that its effect can only be ephemeral, since it is promptly converted into adrenoxidase.[*]

Far more efficient, however, is *Yersin and Roux's serum*, which corresponds, in composition, with the auto-antitoxin that accumulates in the blood under the influence of the above-mentioned drugs.[*] The failure of this serum in a large proportion of cases is due to the fact that it only increases the blood's asset in auto-antitoxin, without exciting the adrenal mechanism.[*] As an adjunct to adrenal stimulants, mercury, for example, should prove invaluable.[*]

The main indication is to consider those remedies as sheet-anchor which will evoke the strongest weapons that the body can muster. Mercury has been used extensively in plague, but either as a purgative, or combined, or given simultaneously with agents which counteract its beneficial effects. H. Lorans[57] states that patients "show toleration for large doses of sublimate, taking as much as $1^{1}/_{2}$ grains (0.1 gm.) in twenty-four hours without signs of salivation or stomatitis. They improve under the action of the drug." This applies likewise to iodine, which has been found of great value by a large number of practitioners. Gujjar, of Bombay,[58] for example, gives the following report of the results obtained with iodine trichloride:—

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[*] *Author's conclusion.*
[57] H. Lorans: Med. News, Dec. 30, 1899.
[58] Gujjar: Indian Med. Record, May 1, 1906.

For February.

STATIONS.	NO. OF CASES.		RECOVERIES.		DEATHS.		PERCENTAGE OF RECOVERIES.	
	With buboes.	Without buboes.	With buboes.	Without buboes.	With buboes.	Without buboes.	With buboes.	Without buboes.
Girgaum.....	41	45	23	45	18	0	56.09	100.
Pydhoni.....	23	64	9	60	14	4	39.1	93.7
Bazargate....	15	26	12	26	3	0	80	100
Total....	79	135	44	181	35	4	55.6	97.03
		214		175		39		

For March.

STATIONS.	With buboes.	Without buboes.	With buboes.	Without buboes.	With buboes.	Without buboes.	With buboes.	Without buboes.
Girgaum.....	110	258	58	252	52	6	52.7	97.6
Pydhoni.....	49	209	26	206	23	3	53.06	98.5
Total....	159	467	84	458	75	9	52.8	98.07
		626		549		84		

Although this report seems extraordinary and makes one wonder why the mortality of plague is so great, the fact remains that it shows at least that iodine is not harmful in the disease and that the indications which I submit are warranted.

The use of adrenalin chloride has been extolled by Choksy, of Bombay,[illegible] for cardiac failure in plague. He states that "a marked change for the better was soon apparent in the condition of the patients after they were put under adrenalin." I have shown under "Antitoxin" that all sera were in reality the auto-antitoxin of the animal from which the "antitoxin" is obtained. The value of Yersin and Roux's serum suggests itself under these conditions.

The second indication is to restore the normal caliber of the arterioles by stimulating powerfully the sympathetic center. A careful selection of drugs is necessary here. Excessive constriction of these vessels would greatly diminish the volume of blood admitted to the capillaries. It is advisable, therefore, to avoid opium, the coal-tar products, and all analgesics in fact, as these agents reduce pain by causing marked constriction of the arterioles, which would mean added torpor of the lymph-stream and freedom to the plague bacilli to pullulate.* The aim should be to employ an agent capable of compensating for the reduced caliber by an augmentation of the propulsive activity of the vessel.* We have precisely such an agent in *atropine*, which, besides, is capable of stimulating the test-organ and therefore of increasing the volume of auto-antitoxin in the blood.[*] A dose of $^1/_{100}$ grain (0.00065 gm.) with each dose of sodium iodide suggests itself, but much larger doses would probably be necessary to overcome the torpor of the sympathetic center due to the toxin.[*]

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* *Author's conclusion.*

[illegible] Choksy: Indian Med. Gazette, Apr., 1905.

Atropine has likewise been used in plague, but practically always with drugs capable of counteracting its action. Where such has not been the case, however, it has shown distinctly its value. Thus, R. Row[**] says that in August and September, 1899, he tested atropine in the treatment of 97 cases of plague. To these he adds the 291 cases of Major R. J. Windle, and 78 cases treated by Dr. A. Turkhud in November and December. The most prominent feature observed in the treatment was the condition of the bubo, which either subsided completely or remained as a hard nodule, which, in some cases when cut into, showed a mass of slough with hardly any pus. Personal cases gave scarcely 14 per cent. of suppurations, and it was interesting to note that the smaller the dose of atropine administered, the more frequently suppurations were found. Some cases not treated with atropine showed 84 per cent. of suppurations. The localization of the bubo indicated a favorable termination of the disease. As to the size of the dose, Dr. Row states 6 drops of the liquor atropinæ sulph. failed in some instances to cause contraction of the pupil, and that such cases, as a rule, fared badly. From my viewpoint, the sympathetic center had been paralyzed by the toxin, and reacted no more to atropine than to any other agent—except, perhaps, mercury.

The third feature of the treatment is to maintain the fluidity of the blood and lymph, *i.e.*, their osmotic properties.[*] This factor is of especial importance in all diseases in which, as in plague, the lymphatic system is primarily involved, since any degree of abnormal viscidity of the lymph, by slowing the speed of the current, retards transmission of the pathogenic germs to the blood, where they are most readily destroyed.[*] The indications outlined on page 1367 are eminently applicable in the present connection.

Prophylaxis.—In the light of the above facts, to protect the body against plague infection, the protective activity of the adrenal system should be increased by remedies able to excite the test-organ.[*] Haffkine's prophylactic fluid owes its properties to such an action,[*] while the serum of Yersin and Roux is the antitoxin itself. *Thyroid gland,* 2 grains (0.13 gm.) after meals, suffices to increase markedly the auto-antitoxin in the blood;[*] the *iodides of mercury* and also *iodine* and its preparations are both, we have seen, capable of enhancing powerfully the efficiency of the body's auto-protective mechanism.[*]

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[*] *Author's conclusion.*

[**] R. Row: Lancet, May 19, 1900.

INDEX TO VOLUME SECOND.

Abdominal typhus, 1758.

Acetanilid, 1290; physiological action, 1290; therapeutics, 1293; untoward effects and poisoning, 1291.

Aconite, 1347; physiological action, 1347; therapeutics, 1349; untoward effects and poisoning, 1347.

Active agent of the oxidizing substance, adrenal secretion as the, 841.

Active principle of the adrenal secretion as the active agent of the oxidizing substance, 841.

Active principle of adrenoxidase as the dynamic element of life, 933, 941; as the ferment of the coagulation ferment, and rennin as "fibrinogen proper," 869; as the ferment of pepsin, 875; as the ferment of ptyalin, amylopsin, lipase and maltase, and of the diastase which converts glycogen into sugar, 862; as the ferment of trypsin, 857.

Adenitis, malignant, 1807.

Adrenal active principle as the dynamic element of life, 885; as the ferment of ferments, 851, 878.

Adrenal extractives, 1169; physiological action, 1169; poisoning, 1173; therapeutics, 1175.

Adrenal secretion as the active agent of the oxidizing substance, active principle of the, 841; as the blood constituent which takes up the oxygen of the air, 806; as the constituent of hæmoglobin, 825.

Adrenal system as immunising mechanism, and cancer, 1389; as the auto-immunising mechanism of the organism, 1072; convulsive diseases due to hypoacticity of, 1426; disorders due to hyperactivity of the, 1548; in the catarrhal and nervous disorders of the respiratory tract, 1601; in the diseases of the alimentary canal, 1720; in diseases of the blood, 1770; in infections of the lungs, 1606, 1656; in infections of the lymphatic system, 1735; pain-causing disorders due to hypoactivity of the, 1400.

Adrenalin, 1169.

Adrenals in respiration, secretion of the, 801; thyroid apparatus and anterior pituitary combined as the auto-immunising mechanism of the organism, 1072; pituitary body as the governing center of the, 1608.

Adreno-thyroid center, posterior pituitary the seat of the, 1125.

Adrenoxidase, 850; active principle of, as the dynamic element of life, 933, 941; adrenal secretion as the active agent of, 841; as the albuminous constituent of hæmoglobin, 822; as a constituent of enterokinase and of trypsin, 851; as the ferment of the coagulation ferment, 869; as the ferment of pepsin, active principle of, 875; as the ferment of ptyalin, active principle of, 862; as a respiratory constituent of all organisms, 812; as "secretin," 857; hydrolytic ferments as compound bodies containing a zymogen, nucleo-proteid and, 878; in the functions of the nerve-cell, 915; in the nervous elements as a cause of pain, 1367; red corpuscles as storage-cells for, 828.

Adrenoxidase plus nucleo-proteid as enterokinase, 857.

Albuminous constituent of hæmoglobin, oxidising substance (oxidase) as the, 822.

Alcohol, 1328; physiological action, 1328; therapeutics, 1335; untoward effects, 1330; valueless as a food, 1335.

Alimentary canal, adrenal system in the diseases of the, 1720.

Alkaline carbonates, 1367.

Alkaline salts, 1370.

Alveolar sarcoma, 1405.

Amyl nitrite, 1350; acute poisoning, 1352; physiological action, 1350; therapeutics, 1353.

Amylopsin, active principle of adrenoxidase as the ferment of, 862.

Anæmia, 1771; definition, 1771; due to hæmorrhage, 1774; symptomatology, pathology, and pathogenesis, 1771; treatment, 1777.

Anæmia, idiopathic, 1778.
Anæmia, pernicious, 1778.
Anæsthesia, surgical, excitation of the vasomotor center and, 1293.
Analgesics, sympathetic center in action of, 1270.
Angina pectoris, 1565; definition, 1565; pathogenesis, 1566; symptoms, 1565; treatment, 1570.
Angiosarcoma, 1405.
Anterior pituitary as a lymphoid organ, 1037; thyroid apparatus and adrenals combined as the auto-immunising mechanism of the organism, 1072.
Antipyrin, 1282; action as an analgesic, 1285; action as antipyretic, 1284; physiological action, 1282; therapeutics, 1289; untoward effects and poisoning, 1286.
Antitoxins, 1177; physiological action, 1181; source and chemical nature of, 1177; therapeutics, 1184; untoward effects, 1182.
Anuria, 1219.
Apocynum, 1225.
Apomorphine, 1380.
Apoplexy, 1573.
Arsenic, 1310; acute poisoning, 1314; chronic poisoning, 1313; physiological action, 1310; therapeutics, 1317; untoward effects, 1313.
Arteriofibrosis, 1548.
Arteriosclerosis, 1548; definition, 1548; pathogenesis and pathology, 1548; symptoms, 1548; treatment, 1560.
Asiatic cholera, 1720.
Aspiration pneumonia, 1681.
Asthenic glycosuria, 1597; definition, 1597; pathogenesis and pathology, 1602; symptoms and etiology, 1598; treatment, 1606.
Asthma, 1699.
Asthma, bronchial, 1699; definition, 1699; pathogenesis and pathology, 1701; symptoms, 1699; treatment, 1705.
Asthma, hay, 1709.
Asthma, spasmodic, 1699.
Atheroma, 1548.
Atropine, 1210.
Auto-antitoxin, drugs which enhance the formation of, 1134, 1201.
Auto-protective substance, internal secretions as the body's, 1099.
Autumnal fever, 1758.
Belladonna and atropine, 1210; physiological action, 1210; therapeutics, 1214; untoward effects and poisoning, 1213.
Bilious headache, 1522.
Black death, 1807.
Bleeder's disease, 1791.
Blood, diseases of the, adrenal system in, 1770.
Blood-plasma as homologue of sea-water, 1262.
Breast-pang, 1565.
Bromides, 1338; acute poisoning, 1341; physiological action, 1338; therapeutics, 1342.
Bromism, 1339.
Bronchial asthma, 1699.
Bronchial catarrh, acute, 1692.
Bronchitis, acute, 1692; definition, 1692; etiology and pathogenesis, 1693; symptoms and pathology, 1692; treatment, 1695.
Bronchitis, capillary, 1681.
Broncho-pneumonia, 1681; definition, 1681; etiology and pathogenesis, 1683; symptoms, 1681; treatment, 1685.
Bronzing, hæmoglobin and, 835.
Brucine, 1231.
Bubonic plague, 1807.

Caffeine, 1231.
Calcium, 1372.
Calomel, 1146, 1388.
Cancer, 1390; definition, 1390; pathogenesis and pathology, 1397; prophylaxis, 1422; symptoms, 1391; treatment, 1413.
Cancer, encephaloid, of the mammary gland, 1393.
Cancer, external, 1391.
Cancer immunity, 1425.
Cancer, internal, 1393; of the gall-bladder, 1395; of the intestine, 1396; of the larynx, 1394; of the liver, 1395; of the mammary gland, 1392; of the œsophagus, 1394; of the pancreas, 1395; of the peritoneum, 1396; of the rectum, 1397; of the skin, 1391; of the stomach, 1394; of the tongue, 1393; of the uterus, 1396.
Cancerous cachexia, 1411.
Capillary bronchitis, 1681.
Carbolic acid, 1361.
Carcinoma, colloid, 1404; cylindrical, 1404; granular, 1404; squamous, 1404.
Cardiac dropsy, calomel in, 1388.
Castor oil, 1377.
Catarrh, pollen, 1709.
Catarrh, suffocative, 1681.

Catarrh, summer, 1709.

Catarrhal disorders of the respiratory tract, adrenal system in, 1691.

Catarrhal enteritis, acute, 1737.

Catarrhal enteritis, simple acute, 1750.

Catarrhal pneumonia, 1681.

Catarrhus æstivus, 1709.

Cellular life, potassium in, 1372.

Cerebral apoplexy, 1573.

Cerebral hæmorrhage, 1573; definition, 1573; pathogenesis and pathology, 1576; symptoms, 1573; treatment, 1578.

Chloræmia, 1784.

Chloral, 1318; chronic poisoning, 1322; physiological action, 1318; therapeutics, 1323.

Chloranæmia, 1784.

Chloride of sodium, 1367.

Chloroform, 1294; danger signals, 1298; physiological action, 1294; untoward effects, 1296

Chlorosis, 1784; definition, 1784; etiology and pathogenesis, 1787; symptomatology and pathology, 1784; treatment, 1789.

Cholera algida, 1720.

Cholera Asiatica, 1720; definition, 1720; pathogenesis and pathology, 1723; prophylaxis, 1733; symptoms, 1720; treatment, 1730.

Cholera, dry, 1722.

Cholera, epidemic, 1720.

Cholera, infantile, 1737.

Cholera infantum, 1737; definition, 1737; pathogenesis and pathology, 1738; symptoms, 1737; treatment, 1740.

Cholera maligna, 1720.

Cholera morbus, 1734; definition, 1734; pathogenesis and pathology, 1735; symptoms, 1734; treatment, 1736.

Cholera nostras, 1734.

Cholera siderans, 1722.

Cholera, sporadic, 1734.

Coca and cocaine, 1232; physiological action, 1232; therapeutics, 1233; untoward effects and poisoning, 1235.

Cocainism, 1237.

Codeine, 1281.

Colitis, mucous, 1753.

Colitis, ulcerative, 1753.

Colloid carcinoma, 1404.

Common sensibility, neural lobe of the pituitary as the seat of, and as the general motor center, 995.

Congenital syphilis, 1806.

Conjugal glycosuria, 1597.

Convallaria, 1225.

Convulsions, infantile, 1472.

Convulsive diseases due to hypoactivity of the adrenal system, 1428.

Coryza, idiosyncratic, 1709.

Creosote, creosote carbonate, gualacol and gualacol carbonate, 1357; physiological action, 1357; therapeutics, 1360; untoward effects and poisoning, 1360.

Croton oil, 1377.

Croupous pneumonia, 1659.

Cutaneous sarcoma, 1392.

Cylindrical carcinoma, 1404.

Death in infections, absence of mineral salts as cause of, 1370.

Deciduoma malignum, 1404.

Defensive properties of the blood, drugs which enhance the, 1134.

Deglutition pneumonia, 1681.

Diabète bronzé, 1597.

Diabète maigre, 1597.

Diabetes decipiens, 1597.

Diabetes mellitus, 1583; definition, 1583; diet, 1595; pathogenesis and pathology, 1585; symptoms, 1583; treatment, 1591.

Diaphoretics, 1380; physiological action, 1380; therapeutics, 1383; untoward effects and acute poisoning, 1382.

Diarrhœa, acute, 1750.

Diarrhœa, chronic, 1753.

Diarrhœa, dyspeptic, 1742.

Diarrhœa, infantile, 1742.

Diarrhœa, summer, 1742.

Diarrhœa, tropical, 1753.

Diastase which converts glycogen into sugar, active principle of adrenoxidase as the ferment of, 862.

Digitalis, 1215, 1387; physiological action, 1215; therapeutics, 1221; untoward effects and poisoning, 1219.

Disorders due to hyperactivity of the adrenal system, 1548.

Diuresis, 1219.

Diuretics, 1387.

Drugs which become constituents of the tissue-cells, 1346.

Drugs which enhance the defensive properties of the blood, 1134.

Drugs which promote the formation of auto-antitoxin, 1261.

Dry cholera, 1722.

Dynamic element of life, active principle of adrenoxidase as the, 933, 941; adrenal active principle as the, 935.

Dyspeptic diarrhœa, 1742.

Eclampsia, infantile, 1472.
Eclampsia, puerperal, 1473.
Ehrlich's side-chain theory, 1177.
Emaciating diabetes, 1597.
Emetics, 1378; physiological action, 1378; therapeutics, 1380; untoward effects and poisoning, 1379.
Encephaloid cancer of the mammary gland, 1393.
Endarteritis chronica deformans, 1548.
Enteric fever, 1758.
Enteritis, acute, 1750; definition, 1750; pathogenesis and pathology, 1751; symptoms, 1751; treatment, 1752.
Enteritis, acute catarrhal, 1737.
Enteritis, chronic, 1753; definition, 1753; pathogenesis and pathology, 1754; symptoms, 1753; treatment, 1755.
Enteritis, simple acute catarrhal, 1750.
Entero-colitis, acute, 1743.
Entero-colitis, chronic, 1753.
Enterokinase, adrenoxidase as a constituent of, 851.
Enterokinase, adrenoxidase plus nucleo-proteid as, 857.
Epidemic, cholera, 1720.
Epilepsy, 1454; definition, 1454; etiology, 1457; pathogenesis, 1457; pathology, 1454; symptoms, 1454; treatment, 1465.
Epilepsy, Jacksonian, 1457, 1465; treatment, 1472.
Epilepsy, major, 1455.
Epilepsy, minor, 1454.
Epilepsy, reflex, treatment, 1472.
Epileptoid disorders, 1472.
Epinephrin, 1169.
Epithelioma, 1404.
Ergot, 1383; physiological action, 1383; therapeutics, 1386; untoward effects and poisoning, 1385.
Ergotism, chronic, 1385.
Erythrol tetranitrate, 1357.
Ether, 1299; danger signals, 1302; physiological action, 1299; untoward effects, 1301.
Ether pneumonia, 1670.
Eucalyptus, 1246.
Excitation of the vasomotor center and surgical anæsthesia, 1293.

Falling evil, 1454.
Falling fits, 1454.
Falling sickness, 1454.
Ferment of the coagulation ferment, active principle of adrenoxidase as the, 869.
Ferment of ferments, adrenal active principle as the, 851, 878.
Ferment of pepsin, active principle of adrenoxidase as the, 875.
Ferment of ptyalin, amylopsin, lipase, and maltase, and of diastase which converts glycogen into sugar, active principle of adrenoxidase as the, 862.
Ferment of tissue-cells, leucocytic ferments as the intracellular, 907.
Ferment of trypsin, active principle of adrenoxidase as the, 857.
Ferments, leucocytic, as the intracellular ferments of tissue-cells, 907.
Fever, 1201.
Fibrinogen proper, rennin as, 869; zymogen of, 869.
Fibrinous pneumonia, 1659.
Fright glycosuria, 1597.

Gall-bladder, cancer of, 1395.
Gastro-enteritis, acute, 1742.
General motor center, neural lobe of the pituitary as the seat of common sensibility and the, 995.
Giant-celled sarcoma, 1405.
Glycogen into sugar, diastase which converts, 862.
Glycosuria, 1583.
Glycosuria, asthenic, 1597.
Gout, 1500; definition, 1500; pathogenesis, 1503; pathology, 1500; prophylactic treatment of, 1519; symptoms, 1500; treatment, 1514.
Gouty diathesis, 1500.
Granular carcinoma, 1404.
Granulations of leucocytes and adrenoxidase in the functions of the nerve-cell, 915; as the granules (microsomes) of tissue-cells, 896; as the living substance, 885, 927.
Granules of tissue-cells, granulations of leucocytes as the, 896.
Green sickness, 1784.
Guaiacol, 1360.
Guaiacol carbonate, 1360.

Hæmoglobin, adrenal secretion as the constituent of, 835; and bronzing, 835; oxidizing substance (oxidase) as the albuminous constituent of, 822.
Hæmophilia, 1791; definition, 1791; etiology and pathogenesis, 1792; symptoms and pathology, 1791; treatment, 1792.
Hæmophilia, sporadic, 1791.
Hay asthma, 1769.
Hay-fever, 1769.

Headache, bilious, 1528; sick, 1527.
Hemicrania, 1522.
Heroin, 1281.
Herpes zoster, 1524.
Homatropine hydrobromide, 1215.
Hydrastinine, 1396.
Hydrastis, 1396.
Hydrolytic ferments as compound bodies containing a zymogen, nucleoproteid and adrenoxidase, 878.
Hydrophobia, 1486.
Hyoscyamine sulphate, 1215.
Hyoscyamus, 1215.
Hyperactivity of the adrenal system, disorders due to, 1548.
Hyperæsthetic rhinitis, 1709; definition, 1709; etiology and pathogenesis, 1711; prophylaxis, 1712; symptoms, 1709; treatment, 1712.
Hypnotism, 1265.

Idiopathic anæmia, 1778.
Idiopathic tetanus, 1441.
Idiosyncrasy, 1209.
Idiosyncratic coryza, 1709.
Ileo-colitis, acute, 1750.
Immunity, 1367; in cancer, 1425.
Immunizing functions, pituitary body as the governing center of the body's, 960.
Infantile cholera, 1737.
Infantile convulsions, 1472; treatment, 1473.
Infantile diarrhœa, 1742; definition, 1742; pathogenesis and pathology, 1743; symptoms, 1742; treatment, 1748.
Infantile eclampsia, 1472.
Infectious diseases of the lungs, adrenal system in, 1608, 1658.
Intermittent tetanus, 1429.
Internal secretions as the body's autoprotective substance, 1099.
Intestinal catarrh, acute, 1750.
Intestine, cancer of the, 1396.
Intracellular ferments of tissue-cells, leucocytic ferments as the, 907.
Iodides, 1159.
Iodine and the iodides, 1159; acute poisoning, 1167; physiological action, 1159; therapeutics, 1166.
Iodism, 1163.
Ipecac, 1280.
Iron, 1247; physiological action, 1247; poisoning, 1249; therapeutics, 1249.

Jaborandi, 1280.
Jacksonian epilepsy, 1457, 1465; treatment, 1472.
June cold, 1709.

Larynx, cancer of, 1394.
Leucocytes, anterior pituitary as a lymphoid organ in which the products of, are exposed to the test-organ, 1037; as the distributors of remedies and poisons, 1027; as the granules (microsomes) of tissue-cells, granulations of, 896; as the purveyors of the thyroid and parathyroids, and as the secreting cells of these organs, 1057; as tissue builders, 885; granulations of, and adrenoxidase in the functions of the nerve-cell, 915; granulations of, as living substance, 885, 927.
Leucocytic ferments as the intracellular ferments of tissue-cells, 907.
Life, active principle of adrenoxidase as the dynamic element of, 933, 941; adrenal active principle as the dynamic element of, 885.
Lipase, active principle of adrenoxidase as the ferment of, 862.
Lithæmia, 1500.
Lithium, bromides of, 1338.
Liver, cancer of the, 1395.
Living substance, granulations of leucocytes as the, 885, 927.
Lobar pneumonia, 1659.
Lobular pneumonia, 1681.
Lockjaw, 1437.
Lues, 1795.
Lues venerea, 1796.
Lungs, adrenal system in the infectious diseases of the, 1608, 1658.
Lymphatic system, adrenal system in infections of the, 1786.
Lymphoid organ, anterior pituitary as a, 1037.
Lymphosarcoma, 1405.

Magnesium citrate, 1377.
Magnesium sulphate, 1377.
Malignant adenitis, 1807.
Maltase, active principle of adrenoxidase as the ferment of, 862.
Mammary gland, cancer of, 1392.
Marine salts as participants in the defensive functions, 1367.
Mechanism of vasodilation and its relations to organic function, 1115.
Mercury, 1146; acute poisoning, 1165; physiological action, 1146; therapeutics, 1157; untoward effects, 1150.
Mercurialism, 1152.
Microsomes of tissue-cells, granulations of leucocytes as the, 896.

Migraine, 1522; definition, 1522; etiology and pathogenesis, 1525; prophylaxis, 1526; symptoms and pathology, 1522; treatment, 1526.
Morbus caducus, 1454.
Morbus sacer, 1454.
Morbus virgineus, 1784.
Morphine, 1272.
Morphinism, 1276.
Morphinomania, 1276.
Motor center, general, neural lobe of the pituitary as the seat of common sensibility and as the, 995.
Mucous colitis, 1753.
Mustard, 1379.

Need of a secretion to account for the respiratory process, 801.
Nerve-cell, granulations of leucocytes and adrenoxidase in the functions of the, 915.
Nerve-paths from the pituitary to the spinal cord, 973.
Nervous disorders of the respiratory tract, adrenal system in, 1691.
Nervous fever, 1758.
Neural lobe of the pituitary as the seat of common sensibility and as the general motor center, 995; as the seat of the sympathetic center, 962.
Neuralgia, 1529.
Neuritis, including neuralgia, tic douloureux, sciatica and zona (shingles, herpes zoster), 1529; definition, 1529; etiology and pathogenesis, 1533; general pathology, 1536; symptoms and pathology, 1530; treatment, 1541.
Nitre, 1353.
Nitroglycerin, 1354; physiological action, 1354; therapeutics, 1356; untoward effects and poisoning, 1355.
Nitrous oxide, 1303; danger signals, 1306; physiological action, 1303; untoward effects, 1306.
Nucleo-proteid and adrenoxidase, hydrolytic ferments as compound bodies containing a zymogen, 878.
Nucleo-proteid plus adrenoxidase as enterokinase, 867.

Œsophagus, cancer of, 1394.
Opium and morphine, 1272; action as analgesic, 1273; action as hypnotic, 1275; acute poisoning, 1278; physiological action, 1272; therapeutics, 1279.
Opsonins, 1083; as the thyroid secretion, 1094.
Organic function, vasodilation and its relations to, 1115.
Oxidase as a respiratory constituent of all organisms, 812; as the albuminous constituent of hæmoglobin, 822.
Oxidising substance (oxidase) as a respiratory constituent of all organisms, 812; as the albuminous constituent of hæmoglobin, 822; red corpuscles as storage-cells for the, 823.
Oxygen of the air, adrenal secretion as the blood constituent which takes up the, 805.
Oxytocics, 1383.

Pain, adrenoxidase in nervous elements as a cause of, 1267.
Pain-causing disorders due to hypoactivity of the adrenal system, 1490.
Pancreas, cancer of the, 1395.
Paraldehyde, 1323; poisoning, 1324.
Parathyroids, leucocytes as the purveyors of the, 1057.
Peach cold, 1709.
Pepsin, active principle of adrenoxidase as the ferment of, 875.
Peritoneum, cancer of, 1396.
Pernicious anæmia, 1778; definition, 1778; etiology and pathogenesis, 1781; symptoms and pathology, 1778; treatment, 1782.
Pertussis, 1716; definition, 1716; etiology and pathogenesis, 1717; symptoms, 1716; treatment, 1717.
Phosphorus, 1250; chronic poisoning, 1257; physiological action, 1250; therapeutics, 1257; untoward effects and acute poisoning, 1251.
Phthisis, 1609.
Physiological excitant of the test-organ, thyro-parathyroid secretion as the, 1067.
Pilocarpine, 1280.
Pituitary body as a nerve-center, 966; as the governing center of the adrenals and as the thermogenic and respiratory center, 1006; as the governing center of the body's immunising functions, 960; nerve-paths from the, to the spinal cord, 973; neural lobe of the, as the seat of common sensibility and as the general motor center, 995; neural lobe of the, as the seat of the sympathetic center, 962.
Plague, 1807; definition, 1807; etiology and pathogenesis, 1810; prophylaxis, 1813; symptoms, 1808; treatment, 1810.

Pneumonia, 1659; complications, 1667; definition, 1659; etiology and pathogenesis, 1667; symptoms and pathology, 1660; treatment, 1672.
Pneumonia, aspiration, 1681.
Pneumonia, broncho-, 1681.
Pneumonia, catarrhal, 1681.
Pneumonia, croupous, 1659.
Pneumonia, deglutition, 1681.
Pneumonia, fibrinous, 1659.
Pneumonia, lobar, 1659.
Pneumonia, lobular, 1681.
Pneumonitis, 1659.
Poisoning, acetanilid, 1291; aconite, 1347; adrenalin, 1173; alcohol, 1330; amyl nitrite, 1352; antipyrin, 1286; arsenic 1313; atropine, 1213; belladonna, 1213; bromide, 1341; chloral, 1322; chloroform, 1296; coca and cocaine, 1235; creosote, 1359; digitalis, 1219; ergot, 1385; ether, 1301; iodine, 1163, 1167; iron, 1249; mercury, 1150, 1152; morphine, 1276, 1278; nitrous oxide, 1306; nitroglycerin, 1355; opium, 1278; paraldehyde, 1324; phosphorus, 1251, 1257; pilocarpine, 1382; quinine, 1243; strophanthus, 1224; strychnine, 1229; sulphonal, 1325; trional, 1325; veratrum viride, 1344.
Pollen catarrh, 1709.
Posterior lobe of the pituitary the seat of the adreno-thyroid center, 1125; as the seat of common sensibility and as the general motor center, 995.
Potassium and sodium tartrate, 1377.
Potassium bitartrate, 1377.
Potassium, bromides of, 1338.
Potassium in cellular life, 1372.
Potassium phosphates, 1367.
Potassium tartrate, 1377.
Pox, 1795.
Present status of therapeutics, 1113.
Progressive pernicious anæmia, 1778.
Ptyalin, active principle of adrenoxidase as the ferment of, 862.
Puerperal convulsions, 1473.
Puerperal eclampsia, 1473; definition, 1473; etiology and pathogenesis, 1474; symptoms and pathology, 1473; treatment, 1480.
Pulmonary tuberculosis, 1609; definition, 1609; etiology and pathogenesis, 1628; prophylaxis, 1656; symptoms and pathology, 1610; treatment, 1639.
Purgatives, 1374; physiological action, 1374; therapeutics, 1377.
Quinine, 1240; physiological action, 1240; therapeutics, 1245; untoward effects and poisoning, 1243.

Rabies, 1486; definition, 1486; etiology and pathogenesis, 1489; incubation of, 1486; paralytic period, 1488; premonitory symptoms of, 1486; prophylactic treatment, 1492; spasmodic stage, 1487; symptoms and pathology, 1486; treatment of developed, 1496.
Ragweed fever, 1709.
Rectum, cancer of, 1397.
Red corpuscles as storage-cells for the oxidising substance, 828.
Remedies used to influence special organs, 1373.
Remedies which depress the functions of the adrenal, vasomotor, and sympathetic centers, 1307.
Rennin as "fibrinogen proper," 869.
Respiration, secretion of the adrenals in, 801.
Respiratory center, pituitary body as the, 1008.
Respiratory process, need of a secretion to account for the, 801.
Respiratory tract, catarrhal and nervous disorders of the, adrenal system in the, 1691.
Rhinitis, hyperæsthetic, 1709.
Rose cold, 1709.
Round-cell sarcoma, 1405.

Salicylates, 1282.
Salicylic acid, 1282.
Saline purgatives, 1377.
Saline solution, 1367, 1387.
Sarcoma, alveolar, 1405; angio-, 1405; cutaneous, 1392; giant-celled, 1405; lympho-, 1405; round-celled, 1405; spindle-celled, 1406.
Sciatica, 1532.
Scirrhous cancer of the mammary gland, 1392.
"Secretin," adrenoxidase as, 857.
Secretion of the adrenals in respiration, 801.
Secretion to account for the respiratory process, need of a, 801.
Sensitising substance of all cells, thyro-parathyroid secretion as the, 1087.
Shingles, 1534.
Shock glycosuria, 1597.
Sick headache, 1522.
Skin cancers, 1391.
Sleep, 1259.

Sleep center, sympathetic center as the, 1259.
Sodium bicarbonate, 1372.
Sodium, bromides of, 1338.
Sodium chloride, 1368; contraindications, 1372; therapeutics, 1369; untoward effects, 1372.
Sodium phosphates, 1367.
Sodium sulphate, 1372, 1377.
Source and chemical nature of antitoxins, 1117.
Sparteine, 1225.
Spasmodic asthma, 1699.
Spindle-celled sarcoma, 1405.
Sporadic cholera, 1734.
Squamous carcinoma, 1404.
Squill, 1388.
Status epilepticus, 1456; treatment of, 1471.
Stenocardia, 1565.
Stomach, cancer of, 1394.
Storage-cells for the oxidizing substance, red corpuscles as, 828.
Stramonium, 1215.
Stricto-dilators, cranial, in organic function, 1186.
Strophanthus, 1222; physiological action of, 1222; therapeutics, 1224; untoward effects and poisoning, 1224.
Strychnine, 1225; physiological action, 1225; poisoning, 1229; therapeutics, 1230.
Suffocative catarrh, 1681.
Sugar, diastase which converts glycogen into, 862.
Sulphonal, 1324; poisoning, 1325.
Summer catarrh, 1709.
Summer diarrhœa, 1742.
Suprarenalin, 1169.
Surgical anæsthesia, excitation of the vasomotor center and, 1293.
Sweet spirit of nitre, 1383.
Sympathetic center as the intermediary through which analgesics produce their effects, 1270; as the sleep center, 1259; neural lobe of the pituitary as the seat of the, 962.
Sympathetic constrictors and the cranial stricto-dilators in organic function, 1185.
Syphilis, 1795; congenital, 1806; definition, 1795; etiology and pathogenesis, 1796; symptoms, 1796; treatment, 1804.

Test-organ, adreno-thyroid center as intermediary of impulses to adrenals and thyroid, 1125; anterior pituitary as a lymphoid organ in which the products of leucocytes and any drug, poison, or toxin these cells may contain are exposed to the, 1087; thyroparathyroid secretion as the physiological excitant of the, 1087.
Tetanilla, 1429.
Tetany, 1429; definition, 1429; etiology and pathogenesis, 1430; symptoms and pathology, 1429; treatment, 1434.
Tetanus, 1437; definition, 1437; etiology, 1440; pathogenesis, 1438; prophylactic treatment, 1444; symptoms and pathology, 1437; treatment, 1446.
Tetanus, idiopathic, 1441.
Tetanus neonatorum, 1441.
Tetanus, traumatic, 1440.
Therapeutics, internal secretions as the foundation of rational, 1112; present status of, 1113.
Thermogenic center, pituitary body as the, 1008.
Thyroid, leucocytes as the purveyors of the, 1057.
Thyroid apparatus, anterior pituitary and adrenals combined as the auto-immunizing mechanism of the organism, 1072.
Thyroid extract, 1139; physiological action, 1139; therapeutics, 1144; untoward effects, 1142.
Thyro-parathyroid secretion as the sensitizing substance of all cells, 1087.
Tic douloureux, 1531.
Tissue-cells, granulations of leucocytes as the granules (microsomes) of, 896.
Tissue-cells, leucocytic ferments as the intracellular ferments of, 907.
Tongue, cancer of, 1393.
Toxic glycosuria, 1597.
Tracheobronchitis, 1692.
Traumatic glycosuria, 1597.
Traumatic tetanus, 1440.
Trional, 1325; poisoning, 1325.
Tropical diarrhœa, 1753.
Trypsin, active principle of adrenoxidase as the ferment of, 857; adrenoxidase as a constituent of, 851.
Tuberculosis, pulmonary, 1609.
Typhoid fever, 1758; definition, 1758; pathogenesis and pathology, 1761; prophylaxis, 1763; symptoms, 1758; treatment, 1764.
Typhus, abdominal, 1758.

Ulcerative colitis, 1753.
Uricæmia, 1500.
Uterus, cancer of, 1396.

Vasodilation and its relations to organic function, 1115.

Vasomotor center, excitation of, and surgical anesthesia, 1283.

Veratrum viride, 1343; acute poisoning, 1344; physiological action, 1342; therapeutics, 1346; untoward effects, 1344.

Water as a diuretic, 1387.

Whooping-cough, 1710.

Zinc sulphate, 1370.

Zona, 1534.

Zymogen, nucleo-proteid and adrenoxidase, hydrolytic ferments as compound bodies containing a, 678.

Zymogen of "fibrinogen proper," 669

SUPPLEMENT.

DISEASES IN WHICH ONE OR MORE GLANDULAR PRODUCTS, GIVEN ALONE OR WITH FAMILIAR DRUGS, HAVE GIVEN BETTER RESULTS THAN THE USUAL THERAPEUTIC MEASURES.

CLINICAL experience has shown that certain organic products are not only valuable additions to our therapeutic resources, when used rationally, *i.e.*, not empirically as is too often the case, but also that in the majority of acute diseases, particularly in infectious disorders, their life-saving powers are unequaled by any agent at our command. No one who has witnessed the effects of adrenalin or of the liquor hypophysis injections in what I have termed the "terminal hypoadrenia" of acute infections, would question this statement. There are other disorders encountered in daily professional work, however, in which rational organotherapy, not necessarily alone, but often in conjunction with well directed pharmaceutical agents, is surprisingly helpful. The present supplement has for its object to review succinctly, the endocrinological treatment either alone, or in conjunction with our familiar remedies, of the various disorders in which it has positively enhanced the efficiency of our older measures. Most of the indications given are based on personal experience; others on that of colleagues who had accepted personal suggestions.

The small number of endocrin products used may cause surprise; indeed, I must confess anew, disagreement with those who see "internal secretions" in practically every organ. As the nine editions of the present work have served to emphasize ever since January, 1903, *bona fide* internal secretions are limited, from my viewpoint, to very few structures, whose hormones are as widely distributed as their functional importance is great. This fact has caused me to interpret the clinical application of organic products in a different light from that of observers other than those who have followed my teachings. Indeed, it has enabled me to do what no one else even attempts to do with the prevailing medley of doctrines concerning the physiological action of the various true hormones, viz., to explain *how* they produce their effects in each disorder for which they are recommended. The *fact* that my interpretations of endocrin functions enables me to carry out this program in such an aggregate of disorders, without "straining a point" in any instance, sufficiently demonstrated their strength.

The subject of *arteriosclerosis*, which has assumed the first place among chronic diseases, as destroyer of the human race, and of *influenza* which won the same title among the acute diseases in 1918, are also interpreted differently—as they should be, with the ductless glands as prominent *factors* in the pathogenesis and treatment of these diseases. *Mental diseases* have also held sway, against professional efforts, because, from my viewpoint, the cardinal influence of the endocrins in their development and perpetuation had been ignored. Their pathogenesis and treatment on endocrin lines is also summarized in this supplement. Of course, considerable additional experience and study will be required to place all these practical applications on a permanent footing, for we are but on the threshold of a science of therapeutics the development of which will require united effort.

Abortion 25

Abscess 20

Acne. Treatment 782

Many facts tend to indicate that this disorder is due to inadequate autoprotective activity through insufficiency, inherited or acquired, of the endocrins which take part in the defensive processes. This is shown by the efficiency of vaccines in appropriate cases, agents which provoke the formation of antibodies. Frequently, however, a toxemia, often of intestinal origin, exists, to meet which the defensive functions prove inadequate. In all cases, therefore, it is well to examine carefully the patient for any focal disorder, intestinal stasis, tonsillar crypts, pyorrhea, etc., and to eliminate any that may be found. The thyroid is often slightly enlarged, especially in young girls, an indication of an effort to compensate by undue activity. Hence the value of *thyroid gland* in 1-grain (0.065 Gm.) doses, particularly when given with *corpus luteum* in 4-grain (0.26 Gm.) doses in girls. In males, either *suprarenal gland* 2 grains (0.13 Gm.), pituitary or *hypophysis sicca* (U. S. P.) ¼ grain (0.016 Gm.), is to be preferred, in addition to the local and general measures.

Acromegaly. General article, 607, 1018. Treatment, 618.

As emphasized in the present works and elsewhere, the pituitary is not from my viewpoint, a secreting gland. The neural or posterior lobe contains the main nucleus of the sympathetic system and as such acts as the main center of the adrenals and thyroid. In acromegaly the pressure exerted by the anterior lobe; enlarged from any cause, upon the posterior lobes excites the latter and promotes hyperadrenia and hyperthyroidia and, therefore, excessive general metabolism. Hence the general overgrowth which constitutes the disease, but only during its *sthenic* or first stage. The only good results I have obtained were with measures calculated to counteract this glandular erethism: *quinine hydrobromide*, 5 grains (0.3 Gm.) with *ergotin* 1 grain (0.065 Gm.), *t.i.d.*, after meals, and *massage* of the enlarged tissues daily and *rest*. When after a time the overtaxed endocrins break down, the *asthenic* stage appears; then the use of *thyroid gland* 1 grain (0.065 Gm.), *pituitary gland*, post. lobe 1/10 grain (0.006 Gm.), to sustain the vascular tension, and *adrenal gland* 2 grains (0.13 Gm.) are of distinct value. Random medication is dangerous in this disease. *X-rays* over the frontal or frontotemporal areas have given good results in some cases, probably by promoting absorption of the pathogenic neoplasm.

Actinomycosis. Treatment ... 1168

The beneficial action of *potassium iodide* in these cases illustrates the sensitizing action of the thyroid secretion through which the iodide produces its effects. It must, however, be administered in large doses, with *radium* or *X-ray* locally. Operative measures are of course the most efficient where practicable, but the iodides should also be used in large doses to promote the destruction of undiscovered extensions of the fungus. *Thyroid gland* might prove effective where the iodides fail.

Addison's Disease. General article, 19, 20, 97, 1017. Treatment, 103, 514, 770, 782.

As I pointed out in the first edition, *adrenal gland* is the only remedy of value in this disease, but its use should be regulated by the temperature, beginning with 2 grains (0.13 Gm.) twice daily and increasing the dose if needed. Adrenalin is not efficient. If the blood-pressure keeps low 1/10 grain (0.006 Gm.) of *posterior pituitary* should also be given unless the case be far advanced, when a high blood-pressure entails the danger of adrenal hemorrhage. The cause of the disease should be ascertained if possible; if tuberculosis is suspected, *creosote carbonate* 5 grains (0.3 Gm.) in capsules, after meals, is indicated.

Adenitis, Adenopathies. Treatment.

Whichever be the local treatment

instituted, and even if the adenopathy be tuberculous, *thyroid gland*, 1 grain (0.065 Gm.) *t.i.d.*, seems to hasten recovery by sensitizing the pathogenic organisms to the action of antibodies, particularly if the formation of the latter is enhanced by giving also *posterior pituitary* 1/10 grain (0.006 Gm.) and *strychnine*, 1/40 grain (0.0016 Gm.), to enhance metabolic activity. Minute doses of *calomel*, 1/24 grain (0.0027 Gm.), *t.i.d.*, also activate the endocrins, but should not be given with the thyroid. *Sunlight* is itself an active stimulant of the internal secretions owing to their identity as enzymes, and the activating power of heat, solar heat in particular, on them. *X-rays* and *radium* owe their virtues partly to a similar action, while *vaccines* promote endocrin activity by exciting the adreno-thyroid center. All are effective in adenopathies.

Adiposis Dolorosa, Dercum's Disease. Treatment 727

In 1914, I attributed this disorder to dilatation of the arterioles in the painful areas, the resulting infiltration causing their tissues to swell and form the familiar elongated nodules, while the accompanying hyperemia, by exciting the cutaneous sensory terminals, causes the pain. The central lesions from my viewpoint are mainly located in the neural or posterior lobe of the pituitary, which contains the sympathetic center, with relaxation of the arterioles it governs, including those of the adrenals and thyroid, thus inhibiting partially the functions of these organs and lowering metabolism and causing the adiposis. Hence the well grounded advice of Dercum to subdue the pain with the *salicylates*, particularly *acetylsalicylic acid*, which constrict the arterioles, and to insure prolonged *absolute rest*, which decreases the circulatory (arterial) activity in the painful areas. To decrease the adiposis, *thyroid gland* 1 grain (0.065 Gm.) may safely be given, but combined with *suprarenal gland* 2 grains (0.13 Gm.), both *t.i.d.* While the former tends to dilate the vascular system and deplete the sensory areas, the latter synchronizes with the salicylates in promoting constriction of the arterioles.

Adolescence 11

Alcoholism, Chronic, Pathology, 522, 590. Treatment, 1231, 1240, 1258, 1320, 1330.

The craving for stimulants is mainly due to the depression of the endocrins following their abnormal excitation by alcohol overdosage. The stage of excitement which typifies excessive metabolism and high vascular tension, is replaced by virtual failure of the circulation of which the sympathetic (chromaffin) system, which includes the adrenals, sustains the tone, particularly insofar as the arterioles are concerned. Hence the danger of too suddenly withdrawing alcohol in such patients. *Strychnine*, 1/40 grain (0.0016 Gm.), to stimulate the adrenals, *posterior pituitary* 1/10 grain (0.0065 Gm.), to raise the vascular tension, and *suprarenal gland* 2 grains (0.13 Gm.), in one capsule, *t.i.d.*, are efficient unless excitement prevail. In the latter case *hydrobromate of hyoscin*, 1/200 grain (0.0003 Gm.), hypodermically, which owing to its stimulating action of involuntary muscles tends to constrict the dilated arterioles, followed by *potassium bromide* 30 grains (2 Gm.), to inhibit the irritability of nerve centers, should first be administered.

Alopecia, 24. Treatment 734

In some cases of alopecia, even those which show no endocrin stigmata, or in which no apparent nutritional or nervous disorder is discernible, organotherapy sometimes proves helpful. A woman of 30, in perfect apparent health, non-luetic, and of normal weight, personally observed, became in less than one week, a case of alopecia universalis so absolute that not even an eyelash remained. Of a multitude of treatments, pharmaceutical and physical, tried during two years by different dermatologists, the only one that proved effective was *thyroid gland*, 1 grain (0.065 Gm.), *suprarenal gland*, 2 grains (0.13 Gm.), and *massa ferri carb.*) 2 grains (0.13 Gm.), all in one capsule taken after meals. Hyperadrenia is often accompanied by abnormal hair growth, hence the suprarenal gland given, with iron to promote the formation of hemoglobin. An ointment composed of *chrysarobin* 15 grains (1 Gm.), *lanolin* 1 dram (4 Gm.), and *benzoated lard* 7 drams (28 Gm.), was used, a small quantity being rubbed into the scalp only, while for the tender areas, the axillæ, pubis, labia, etc., *liquid petrolatum*, with *massage* of all surfaces, was alone employed. Chrysarobin is very irritating to the eyes, tender skin, etc., and stains linen; care in its use is, therefore, necessary.

Amenorrhea, Treatment 779

The endocrin treatment of these cases depends upon its cause. Delayed appearance of the menses in young girls may be due to infantile or subnormally developed uterus, this in turn being due to hypothyroidia (*q.v.*) with the stigmata of this condition more or less marked; fat, pale and apathetic girls belong to this type—*thyroid gland* 1 grain (0.065 Gm.), *corpus luteum* 2 grains (0.13 Gm.) to excite ovarian activity and *strychnine sulphate* to excite the adrenals and promote peristalsis, are indicated. In some *pituitary gland post. lobe,* 1/10 grain (0.06 Gm.), with 2 grains (0.13 Gm.) of *iron carbonate,* are more efficient, where the blood count, the hemoglobin percentage and the blood-pressure are low.

Anemia, General article, 1771. Treatment, 1777.

As specified in the general article, many etiological factors prevail in this condition. After the primary cause has been carefully sought and removed, nothing is more efficient than pharmaco-endocrin therapy to build up the corpuscular elements and their hemoglobin, since it enables us to contribute what the blood needs. Prompt results are generally obtained by giving after meals, a capsule containing *suprarenal gland* 2 grains (0.13 Gm.) and *posterior pituitary* 1/10 grain (0.006 Gm.), to increase the power of the hemoglobin to become converted into oxyhemoglobin, *strychnine* 1/60 grain (0.001 Gm.), to stimulate the adrenal activity, and *iron and ammonium citrate* 2 grains (0.13 Gm.), to build up the hemoglobin molecule. In some cases pancreatic torpor prevails as shown by distress one or two hours after meals; in such *dilute hydrochloric acid* 10 minims (0.62 c.c.) in one-half glassful of water, using a glass tube, will promote the formation of trypsin.

Anemia, Pernicious. General article, 1778. Treatment, 1783.

This disease is deemed incurable by many, but close analysis indicates that it is because its recognition is delayed until the injury to the blood has reached such proportion that cure can no longer be obtained. We are dealing with an autolytic destruction of the blood-cells, and the cause of the excessive production of antibodies should be sought and removed early. In most cases, the digestive tract is the source of the pathogenic antigens. Given, therefore, a case in which soreness of the tongue and mouth, gastro-intestinal phenomena characterized by remissions and periodical gastralgia, coincide with yellowish pallor and lassitude, a diagnosis of pernicious anemia will practically always be proven to exist by the blood examination. In such cases *organotherapy is contraindicated* particularly thyroid which, by sensitizing the red corpuscles, facilitates their destruction. Hence the fact that *arsenic,* which as shown by Mabille, Ewald, and others, inhibits the functional activity of that gland, is so helpful and even curative when the cause of the toxemia has been completely eliminated in time.

Angina Pectoris. General article, 1565. Treatment, 1570.

The great value of the *nitrites* in this condition is due to the fact that they are direct antagonists to the adrenal secretion. While the latter by exciting all unstriated muscular fibers causes constriction of the arterioles, the nitrites dilate these precapillary vessels. The same effect is indirectly caused by the *iodides* which, by enhancing the functional activity of the thyroid, promote vasodilation. These salts are preferable to the gland therapeutically, because the heart in these cases is seldom normal.

Anorexia Nervosa. Treatment.

In this disorder, characterized by absolute anorexia and aversion for food, with adynamia, dyspnea, vertigo, nausea and vomiting, and which sometimes proved fatal through inanition, pharmaco-endocrin medication may prove the sheet anchor. There is a general vaso-dilation with recession of the blood into the splanchnic area. The *liquor hypophysis*, the fluid extract of the posterior pituitary, injected in 15-minim (0.9 c.c.) doses daily, with *strychnine* orally in 1/40-grain (0.0016 Gm.) doses, to stimulate the adrenals, soon raise the vascular tension and restore the arterial circulation to the tissues. *Forced feeding* with stomach tube, or per rectum, is usually necessary at first.

Anosmia. Treatment.

This condition, which sometimes proves distressing, may often be greatly improved. It may be due to imperfect lubrication, catarrhal inflammation, or ischemia of the olfactory area, the nervous elements in the latter case being insufficiently supplied with blood to take cognizance of olfactory impressions. The central transmission of the latter may also be due to any lesion of the olfactory tract. Treatment of the causative disorder is, of course, essential. All cases that are not due to a destructive lesion are benefited by *strychnine* 1/40 grain (0.0016 Gm.) and *hypophysis sicca* 1/10 grain (0.0065 Gm.), after each meal, which increase metabolic activity and raise the blood-pressure in the olfactory area as elsewhere. The frequent use of a coarse, lukewarm spray of *saline solution* in the nasal cavities to lubricate them and increase local osmosis, is helpful where atrophy exists. Where a history of syphilis, inherited or acquired, is suspected, *thyroid gland* 1 grain (0.065 Gm.) should be added to each dose.

Anthrax 19

Anuria 15

Appendicitis. Treatment.

The vermiform appendix is not, as now taught in text-books, a functionless structure of low vitality. It is rich in lymphoid tissue which undergoes compensatory hypertrophy when the tonsils are removed. Like the latter organs, it secretes a bactericidal fluid and produces phagocytes to keep within safe bounds the contents of the cecum, which is particularly exposed to the accumulation of putrefactive and often toxic materials, besides bacteria and their toxins. The aim should be, therefore, to increase rapidly the blood's asset in antibodies, and, thereby, the bacteriolytic and antitoxic efficiency of the appendical secretion, and also the amount of the latter. When, therefore, appendicectomy can be *safely* postponed, *thyroid gland* 2 grains (0.13 Gm.) every three hours three times, then every four hours when the patient is awake, is often efficient. *Rest in bed* is imperative, with *hot applications* (hot-water bag, poultices, etc.), over the painful area to increase the proteolytic efficiency of its auto-antitoxin and relieve pain. A *milk diet* assists materially the curative process, *sodium chloride* being added as freely as the taste of the patient will allow, *Milk and Vichy*, equal parts, form a palatable drink which tends further to preserve the osmotic properties of the blood. To deprive the patient of fluids, as advised by some, is a mistake, since they—at least milk and water—are absorbed long before the cecum is reached. The bowels should be emptied daily with warm *saline solution* enemata, adding 2 teaspoonfuls of *glycerine* to the pint (500 c.c.) of solution if free action is not obtained.

Arrhythmia 11

Arteriosclerosis. General article, 20, 1548. Treatment, 1606.

This disease having taken the first place among the causes of death, owing to the complications it entails; cardiac disorders, apoplexy, angina pectoris, aneurysms, etc., additional study of its relations to the endocrins, briefly reviewed on page 1548 is presented in greater detail here. As stated I now recognize three types, each of which requires a different treatment.

1. The *adrenal type*, due to overactivity of the adrenals (and, through their hormone, of the thyroid gland also) observed in persons subjected to hard physical exertion, blacksmiths, letter carriers, hod-carriers, bicyclists, etc., with high blood-pressure, exuberance, pains in the calves of the legs, slow full pulse, hard systolic cardiac impulse, "palpitations," muscular pains, hyperchlorhydria, pyrosis, as more or less clearly defined

symptomatology in which the vascular walls are thickened, hyperemic, but not necessarily the seat of degenerative lesions, unless excessive constriction of the vasa vasorum have so reduced the nutrition of certain areas as to cause them.

2. The *autolytic type*, where slowly acting poisons, food proteins, overfeeding, alcohol, the excessive use of coffee, etc., with exaggerated metabolism and focal autolysis in the vascular walls due to the presence *in the blood of an excess of antibodies* evoked therein by the poisons, or by some acute febrile (bacterial) disease. In the overfed we may witness as early symptoms those enumerated above, with flushed face, brilliant eyes, slight precordial pain after a copious meal or exertion, sometimes slight, and general vivacity. This stage in reality corresponds with the active period of an infection which, though relatively short, may do considerable damage to the blood-vessels. The patient then passes into what is erroneously described in some text-books as an early manifestation of first stage, but which in reality is a more or less advanced phase of the disease, in which the contractile power of certain areas of the arterial system are already compromised. When this stage is reached the syndrome recalling neurasthenia develops more or less clearly, *i.e.*, those of a debilitated and unevenly distributed circulation: loss of vigor, lassitude or myasthenia, drowsiness, postural vertigo, faintness, more or less visual disturbances —hemianopsia or even amaurosis— phobias, headache, and dyspnea on exertion.

3. The *denutrition type*, in which in addition to the arterial lesions there is exhaustion of the adrenals and thyroid through the excessive functional activity imposed upon them by the pathogenic toxic, whatever that may be, the patient having then reached what has been termed the "presenile stage" of arteriosclerosis. In some subjects this may develop early, even in those of frugal habit, because their ductless glands, including the thymus, through inherited debility, are unable to bear the least exacerbation of activity, physical, mental and also emotional. In others, again, the ductless glands may have become debilitated through local hemorrhages with resulting functionless areas, as a result of febrile infections of childhood, diphtheria especially. Such cases of denutrition arteriosclerosis are often the prey of tuberculosis and pneumonia. They grow old early because as the wear and tear of life impinges upon their ductless glands, denutrition progresses, including that of the arterial system.

Treatment: This must of course be adjusted to each of the causative disorders.

Adrenal Type.—Such cases yield readily to measures calculated to reduce the functional activity of the adrenals. A less arduous occupation and abstention from meat, coffee, tea, and alcohol (to lower the vascular tension) often suffice. If the vascular tension is high, the condition of the kidneys should be looked into. As a rule, at this time these organs are found normal, though some polyuria may be present. *Spirit of nitrous ether* may then be used in small doses thrice daily to reduce the high tension if it fails to recede after a few days, and also small doses of *sodium bromide* and *chloral* on retiring if the tendency to insomnia persists.

The iodides at this stage are harmful. So are strychnine, digitalis, and tonics in general, most of which stimulate the adrenals and aggravate the trouble.

Proteolytic Type.—Prophylactic measures, a *reduction of proteins*—eliminating meats and eggs—and other harmful food the patient may be indulging in too freely, are necessary. Acidosis is another harmful factor, which a *vegetable diet*, by supplying alkaline salts, tends to counteract and gradually to eliminate. Although the arteries are already damaged, there occurs an active process of repair by insular scleroses so disposed longitudinally as to preserve the contractile activity of the vessels to a remarkable degree.

It is obviously irrational to give the iodides in cases in which the thyroid secretion laden with iodine in organic combination is taking part in the cellular destruction of the arterial walls. No remedies should be administered until the toxic factor, whatever that may be, dietetic, intestinal, bacterial, etc., is eliminated prophylactically. If after a couple of months, the patient does not show the sense of wellbeing which usually follows well addressed prophylactic measures and still shows neurasthenia like symptoms, it is because catabolism and arterial degeneration is still proceeding, owing mainly to hyperplasia of the thyroid. *Arsenic* in small doses, say 3 minims (0.18 c.c.), of Fowler's solution *t.i.d.*, as shown by Mabille and confirmed by Ewald, Heinrich Stern, and others, will then gradually reduce the thyroid erethism. In cases showing actual hyperthyroidia or larval Graves's disease, *ergotin*, or the *coal tars*, are helpful to contract the vascular supply of both the thyroid and adrenals and thus inhibit their secretory activity. It should be remembered that *rest* is an important feature wherever exuberant activity of the ductless glands is in order.

Denutrition Type.—The treatment here is the opposite of that indicated in the foregoing forms. Organotherapy, provided *thyroid* and *adrenal gland* and any other organic product used is given *in small doses*, is of great value. The *iodides* also in small doses, *digitalis*, and *strophanthus* are exceedingly helpful. A *sustaining diet* is an important feature. Besides the thyroid and adrenal preparations already mentioned, some pancreatic product such as *pancreatin* should be added to facilitate intestinal digestion.

Arthritis, Chronic. Treatment.

It is important in these cases to ascertain whether a focus of infection, tonsillar, dental, uterine, intestinal, cystic, etc., exists, when tuberculosis is not present. Elimination of the cause, followed by a course of *iodides* if the heart be diseased, or *thyroid gland* in 1-grain (0.065 Gm.) doses with *iron and ammonium citrate* 2 grains (0.13 Gm.), after meals, *dry hot air* to the affected joints to enhance the bactericidal or proteolytic activity of their antibodies, and the copious drinking of some *alkaline mineral water* sometimes proves very efficient.

Arthritis Deformans. Treatment, 27

Foci of infection are as prolific factors in this as in the chronic form, and the same treatment is indicated. Diseases of the upper respiratory tract, especially sinus and tonsillar infections, are a frequent cause. Small doses of *mercury biniodide*, by stimulating the function of the thyroid and adrenals, will alone sometimes prove effective. *Buttermilk*, one quart daily, acts as an effective diuretic in these cases.

Ascites and Edema. Treatment, 17, 702

Whatever be the cause of ascites, relaxation of the arterioles, with loss of the adrenal principle in all cases is an important feature. Injections of *adrenalin* intramuscularly, 8 minims (0.50 c.c.), rapidly increased to 30 (1.8 c.c.), is we have seen, often a very efficient measure, besides increasing respiratory and cardiac activity. It proves efficient sometimes where tapping fails, and is very helpful after the latter procedure to prevent recurrence of the ascites. The effect may be kept up by giving *suprarenal gland* in 3-grain (0.2 Gm.) doses after meals, provided a reliable preparation is obtained.

Asiatic Cholera. See Cholera Asiatica, this Supplement.

Asphyxia. Treatment 755, 704

By promoting the intake of oxygen, *adrenalin* is very efficient, 10 minims (0.6 c.c.) of the 1 to 1000 solution in one syringeful of *saline solution*, injected slowly into a vein of the left arm. When it reaches the heart it tends also to promote active contraction of the right ventricle, thus causing the venous blood containing the adrenal principle to reach the air cells promptly. In *asphyxia neonatorum*, Mack has obtained resuscitation by injecting the same solution into the stump of the cord, after all other means had failed.

Asthma, Bronchial. General article, 14, 1699. Treatment, 14, 710, 761, 765, 775, 1705.

The use of *adrenalin* 1 to 1000 solution in from 8 to 10 minims, given intramuscularly in a syringeful of saline solution is almost magical in its effects. It acts mainly by counteracting the suboxidation and by promoting the activity of the entire respiratory mechanism. It should be administered, however, only by the physician. The value of the *iodides* in this disorder also shows that another function which includes suboxidation is deficient, viz., metabolism. By promoting thyroid efficiency, the iodides increase metabolic activity and may cure the disease as personal cases have shown. They are best administered with *tincture of belladonna*, 8 minims (0.50 c.c.) to the dose, to sustain the immediate relief afforded and prevent the paroxysms. *Suprarenal gland* in 2-grain (0.13 Gm.) doses after meals, is very helpful when the suboxidation, shown by cold extremities and weak pulse, persists.

Auricular Fibrillation 11

Auricular Flutter 12

Bones, Diseases of. Pathology, 205, 515. Treatment, 710, 711, 775, 787.

In the various osseous disorders of nutrition, *necrotic*, *syphilitic*, or *infectious*, *thyroid gland*, in relatively large doses, 2 grains (0.13 Gm.) *t.i.d.*, after meals, particularly if *calcium lactate* 5 grains (0.3 Gm.) and *thymus gland* 5 grains (0.3 Gm.) are both given twice daily also, to supply the organic phosphorus-laden nucleins needed to build up the calcium phosphate of the osseous tissues, is sometimes of potent aid to the local measures employed. In *tuberculosis* of bones this treatment often activates greatly the *sunlight* treatment which owes its efficiency mainly to the fact that the defensive ferments are activated by heat up to 104° F. In *osteomalacia*, thyroid, which exaggerates catabolism, should be avoided, while *adrenalin* or *liquor hypophysis* injected intramuscularly in from 8- to 15-minim (0.50 to 0.90 c.c.) doses, the former in saline solution, favors anabolism; *thymus gland* and *calcium lactate* in 5-grain (0.3 Gm.) doses to promote the formation of calcium phosphate, completes the building up process. In *osteomyelitis* both phases of metabolism are necessary. Hence the value of *thyroid gland* 2 grains (0.13 Gm.) and *hypophysis sicca* ¼ grain (0.016) twice daily, in addition to the local measures. In *rachitis*, the same treatment is indicated although some do best under *thyroid gland* with *calcium lactate* or the *glycerophosphates of calcium*. In *tuberculous disorders* including *hip-joint disease*, *scoliosis*, etc., *thyroid gland* is very efficient. It sensitizes the pathogenic organisms, besides the tubercle bacillus and contributes directly, therefore, to the curative process, and aids materially *heliotherapy* which, as stated, enhances the activity of the defensive ferments.

Bright's Disease. Treatment, 784, 1383.

Although the exact relationship between the kidney and the endocrine is not known, my own view that its adrenal rests are dynamic centers of catalytic activity, the adrenal ferment serving to excite in this manner renal function, seems to be borne out by the fact that *adrenalin in large* doses, 20 minims (1.25 c.c.) of the 1 to 1000 solution orally three times a day, has been found beneficial by several observers. While it is generally believed that adrenalin is inert in the body when taken orally, this applies only to cases in which the systemic supply is adequate; if deficient, however, enough is taken up from the intestinal canal to make up the deficiency. *Thyroid gland* owing to its antitoxic action in moderate doses, 1 grain (0.065 Gm.) *t.i.d.*, tends to keep down wastes and thus to protect the kidney. Given with *suprarenal gland* 2 grains (0.13 Gm.) in a capsule, and the *liquor ferri et ammonii acetatis* 2 fluidrams (8 c.c.), also *t.i.d.*, general oxidation is improved through improvement of hemoglobin percentage, thus counteracting the secondary anemia, a prominent factor in the lethal trend of the disease.

Bronchiectasis. Treatment.

In this disorder the dyspnea is the result of reduction of the respiratory area due to destruction of the pulmonary alveoli involved in some dilated areas. *Suprarenal gland* sometimes proves helpful by increasing the supply of adrenin. *Strychnine*, by stimulating the adrenals, also increases the oxygen intake. The two may be given together.

Bronchitis, Chronic. Treatment, 1168, 1231, 1239, 1380.

In some cases the bronchial tract acts as an eliminant for products of endogenous origin, particularly where acidosis prevails. In such, *hypodermoclysis*, using but small quantities of *saline solution*, is very efficient. It promotes osmosis, facilitates the circulation of the plasma through the ultimate bronchial capillaries and enhances the elimination of detritus by the kidneys and the bronchial mucosa. This is materially aided by a few days' *reduced* or *milk diet*. Then *thyroid gland* in 2-grain (0.13 Gm.) doses after each meal, reduced to 1 grain (0.065 Gm.) the second week, but giving in addition *creosote carbonate* in capsules in 10-grain (0.6 Gm.) doses, increasing by 5 grains (0.3 Gm.) weekly until 30 grains (2 Gm.) are taken three times daily. The thyroid gland increases the antitoxic efficiency of the blood; creosote also enhances this action, and excites the propulsive activity of the pulmonary arterioles. The *iodides* may be used instead of the thyroid, but are less active. To sustain the beneficial effects after recovery, *strychnine* is the most efficient remedy owing to its stimulating action upon the adrenals. The patient should drink at least 1 quart (liter) of *Vichy mineral water* daily to sustain the osmotic properties of his blood and lymph.

Bronchopneumonia 19, 770

Cancer. General article, 1300. Treatment, 739, 757, 1413.

Painting *adrenalin* solution 1 to 1000 over the growth, if superficial or within reach, relieves pain, arrests or inhibits hemorrhage and tends, by causing vasoconstriction, to promote retrogression. To favor the latter, injections of adrenalin into the growth, after carefully sterilizing the latter, have also been made with advantage. In inoperable sarcoma, the local use tends to check the hemorrhages. The internal use of *thyroid* and *suprarenal gland* improves the likelihood of recovery in cases treated with *X-rays* or *radium*. Some authors have recommended *thymus gland*. I have never used it.

Canities. Treatment.

Whiteness or blanching of the hair is essentially, unless due to dyes and other local factors, a disorder of the sympathetic or in its true sense, the chromaffin system of which the adrenals form part. Hence their pathogenic influence of fright, mental strain, sorrow, etc., in its production in some instances. Under normal conditions, however, premature grayness is an evidence of hypoadrenia, and *suprarenal gland* 2 grains (0.13 Gm.), to enhance general oxidation, *hypophysis sicca* 1/10 grain (0.006 Gm.), to raise the vascular tension and thus improve the peripheral circulation, and *strychnine* 1/60 grain (0.001 Gm.), to enhance the functional activity of the adrenals, and *ferric chloride* ½ grain (0.03 Gm.), to increase the pigmenting activity of the blood, all given together after each meal, is sometimes very efficient. Some cases show stigmata of hypothyroidia; in such cases *thyroid gland* ½ grain (0.03 Gm.) should be added to the capsule. *Massage* of the scalp with *liquid petrolatum*, morning and evening, where the white areas occur, greatly favors the curative process.

Cataract. Treatment.

This disorder, coinciding as it does with senile atrophy of the endocrine, may sometimes, as personally observed in two cases, be arrested, or at least greatly delayed by means of *thyroid gland* ½ grain (0.03 Gm.) with *suprarenal gland* 2 grains (0.13 Gm.) twice daily. The cases of spontaneous absorption by means of *potassium iodide* 5 grains (0.3 Gm.) *t.i.d.*, which is preferable where arteriosclerosis or any cardiac disorder prevails, that have been reported, may be considered as belonging to endocrin therapy since it is through the thyroid that the iodides produce their beneficial effects.

Cerebral Abscess. General article 1573

Cerebral Paralyses of Children. Treatment.

In these disorders which include *infantile spastic paraplegia*, *Little's disease*, Ramsay's *infantile cerebral diataxia*, the *cerebellar ataxia of* children, etc., considerable improvement may be obtained by activating metabolism by means of *thyroid and suprarenal* or *strychnine* in doses adjusted to the age of the child, coupled with *thymus gland* to enhance the nucleinic nutrition of the nerve centers. While the sclerotic foci or other lesions tending to destroy the functions of the primarily affected areas are probably not benefited, there is distinct evidence, as observed in personal cases, of the assumption by the stimulated normal cells, of increased compensative activity, particularly when physical means such as *passive manipulations* of the immobilized limbs or joints, *massage* and *calisthenics* are employed simultaneously to favor the nutrition of the inhibited motor areas.

Cholera Asiatica. General article, 18, 1720. Treatment, 18, 1730.

In keeping with my views, as expressed in the first edition of this work (1903-1907), Drake Brockman (1910), Piovesana (1912) and others, Naame (1914) found striking analogy between the cholera syndrome and adrenal failure. The patients tolerated large doses of *adrenalin*, which he used subcutaneously in doses representing 1/15 to 1/10 grain (0.004 to 0.006 Gm.) of the salt in the 24 hours daily, supplemented by *saline infusions*. Others have confirmed his assertions as to the value of adrenalin.

Choleraic Diarrhea 18

Chorea. Treatment, 773, 788, 1289, 1317, 1323.

The underlying cause is a toxemia of some sort, usually toxic metabolic wastes. These may be produced either through hypermetabolism, the wastes being excessive, or through hypocatabolism, the wastes being inadequately broken down or hydrolyzed. In other words, the endocrins may be overactive or hypoactive. Thus in the chorea of adolescents, the latter may be the case, the increase in wastes not being met by increased or parallel hydrolysis calculated to convert them into eliminable waste products. The chorea of pregnant women, the aged, gouty or rheumatic subjects, toxins due to acute infections and gastrointestinal disorders also belong to this category.

It is often difficult to determine which of the two prevails. In the adolescent type, hypermetabolism may be the underlying factor and *arsenic* the drug indicated to inhibit, with *rest*, the functional stress of the endocrins. In other adolescents, hypothyroidia and hypoadrenia may predominate, the patient being inclined to adiposis and torpor. In such cases, also those due to acute infections, old age, gout, gastrointestinal disorders, the *iodides* or *thyroid* and *suprarenal gland* with *hypophysis sicca* in small doses, to promote the antitoxic functions, aid materially the measures addressed to the causative disorder.

Choreiform Disorders.

As stated under Chorea, the spasmogenic wastes may be due to hypermetabolism or hypocatabolism; the first step, therefore, is to ascertain which of these conditions prevails. In *chorea major*, a few days' *rest* to permit the breaking down of the spasmogenic wastes and their elimination, the free use of *water* to facilitate this process, and perhaps a *saline purgative* to hasten recovery. *Impulsive tic* of long duration seems to resist all forms of treatment which prove effective in recently developed cases; that of chorea, with sustained effort to avoid the grimaces, etc. In the *habit chorea* of young women, autointoxication of intestinal origin is the usual cause of the arterial hyperconstriction. A weekly *saline purgative*, and Fowler's solution of *arsenic*, with a *diet* in which red meats are partaken of sparingly, while water, or better, an alkaline water, especially *Vichy*, is used freely, usually insure prompt recovery. The *complex co-ordinated tics* occur, as a rule, in backward children or semicretins in which the catabolism of toxic wastes is imperfect. Here *saline purgatives* followed by small doses (1 grain—0.065 Gm.—*t.i.d.*) of *thyroid gland*, by simultaneously ridding the intestinal canal of any cause of autointoxication while increasing the activity of the vital process of catabolism, eliminate the cause of the disorder.

Cirrhosis of Liver 41, 43, 347

Constipation. Treatment 1374

The prevailing teaching that the adrenal principle "inhibits" intestinal activity is the outcome of an experimental error, in the sense that the effect of toxic doses in animals is attributed to therapeutic doses in man. "Neither," as Sollmann states in his text-book, "is there any good evidence for the theory of Eppinger, Falta, and Rüdinger, 1909, that epinephrin inhibits the internal secretion of the pancreas." Were it otherwise, we clinicians who employ epinephrin (adrenalin) constantly in relatively large doses intramuscularly would constantly be meeting signs of such inhibitory effects, which is not the case. In truth, a large proportion of the cases of *atonic constipation* met with should be attributed to lack of tone of the intestinal musculature and the resulting deficient peristaltic activity. Hence the value of *strychnine*, an adrenal excitant, particularly when given with *suprarenal gland* and *thyroid gland*, all in small doses, in such cases. The constant use of purgatives, which entails a loss of the adrenal principle with the serum, can gradually be done away with.

Convalescence.

We have seen the important rôle played by the pancreas, adrenals and thyroid in infections, to the extent in fact that at least in respect to the two latter organs, their functional efficiency is considerably impaired. The use of *strychnine* under these conditions is familiar to all as a "tonic"; but it does not always procure the expected results because it merely stimulates organs, the adrenals particularly, that are already exhausted. If, however, there is added *hypophysis sicca* 1/10 grain (0.006 Gm.) and *suprarenal gland* 1 grain (0.065 Gm.), with *thyroid* ½ grain (0.03 Gm.) to compensate for the deficiency of hormones while the enfeebled glands and the cardio-vascular system are recovering their tone, the convalescence, granting that usual hygienic measures are also carried out, will be considerably hastened.

Dementia Præcox 30, 325

Dengue.

This epidemic, infectious fever, probably transmitted by some unidentified mosquito, presents all the characteristics of failure of the sympathetic—the chromaffin system—to which the adrenals belong, with paresis of the arterioles, and flushing of the joints, muscles and sensory terminals as result. Hence the severe pains in the joints and muscles which have caused the disease to be termed also "break-bone fever." The flow of blood into the capillaries being no longer regulated, there may be hemorrhages from the nose, gums, stomach (black vomit-like), intestines, etc., and an erythematous rash in the skin and around the tongue, headache, flushing, conjunctival congestion, adenitis, high fever (reaching sometimes 107° F.). The sensation of burning, the pruritus, and the marked depression that succeeds the disease—which lasts from five to nine days—all indicate the supranormal metabolism to which the tissues are subjected. *Morphine* and the coal-tar products, *antipyrin*, *acetanilide*, or *sodium salicylate*, if preferred, are very efficacious; by exciting the sympathetic center they cause constriction of the arterioles and by inhibiting the excessive flow of blood into the capillaries arrest the morbid phenomena. To curtail the disease: Khoury recommends *adrenalin* 30 minims (1.8 c.c.) orally of the 1 to 1000 solution; but I would regard as more reliable and prompt 10 minims (0.6 c.c.) of adrenalin in one syringeful of saline solution, injected intramuscularly twice daily, or oftener.

Diabetes Insipidus 40

Diabetes Mellitus. General article 36, 1583

Diphtheria. Treatment, 770, 782, 1153, 1184.

While of course *antitoxin* is our sheet-anchor in this disease, it sometimes happens, as personally observed during an epidemic among immigrants on a ship from the Mediterranean upon which I happened to be, that ill-nourished or debilitated children will fail to respond, death, as observed in this instance, making rapid inroads, despite the excellent quality of the antitoxin and the large doses used. The deaths stopped at once, however, when besides the latter *calomel* in 1/12-grain (0.005 Gm.) doses was administered every half-hour to the little patients until green stools occurred. As we have seen, calomel is a powerful stimulant of all endocrins; the glandular hormones secreted in excess, doubtless harmonized with the antitoxin in destroying the pathogenic organisms.

Dysentery, Bacillary 19

Dysmenorrhea. Treatment, 779, 1215, 1289, 1354, 1387.

In dysmenorrhea accompanied with the passage of clots, the use of thyroid, adrenalin or corpus luteum only aggravates the pain by increasing the coagulability of the blood. In such cases, due probably to what might be termed "hyperendocrinia," *sodium bromide* and *sodium bicarbonate*, 15 grains (1 Gm.) each in solution, the former to reduce the sensitiveness of the centers and the latter to alkalinize the blood and reduce its coagulability; also a granule of *atropine* 1/20 grain (0.0005 Gm.) to reduce the sensitiveness of the uterine nerve endings, give good results, when begun the day before the period and repeated every four hours. *Corpus luteum* or *ovarian gland* is useful in some cases in which the ovarian function is deficient, but how to identify such cases, otherwise than by using the preparation empirically is not clear, unless the general condition of the patient, general adynamia, hypoadrenia, etc., be taken as guide.

Eczema. Treatment .. 24, 734, 1383

A diet too rich in proteins for the efficiency of the patient's endocrins, summarizes the status of most cases met in practice. A strict *vegetarian diet*, beginning after one week with *thyroid gland* 1 grain (0.065 Gm.) and *hypophysis sicca* 1/10 grain (0.006 Gm.) to enhance oxidation and catabolism, keeping up the vegetarian diet but omitting the glands three days every other week, often suffice. In infants, the fats should be reduced and small doses, 1/10 to 1/15 grain (0.006 to 0.004 Gm.) of thyroid given twice daily, besides the local treatment.

Endocarditis 33, 345

This disease is one of those in which excessive defensive activity of the endocrins is productive of harm. It is not due as is now taught, to direct infection of the valves or endocardium. Whether simple, malignant, or chronic, it is the result of autolysis of the valves and cardiac tissues by the blood when it contains a marked excess of antibodies, the active agents of which are digestive or proteolytic enzymes, and thyroiodase, as may be the case in any of the causative diseases. Hence the usual presence of the abrasions along the line of contact of the leaflets, their surface, and the wall of the cardiac cavity of the left ventricle, that through which arterial blood circulates with greater vigor than elsewhere in the body owing to the ventricular contractions. The occasional presence of bacteria in the lesions is but an adventitious circumstance of the causative general disease, the vegetations being efforts at local repair.

Endocarditis would occur very infrequently were the blood's fluidity and osmotic properties preserved by the use of *saline solution* in all infections, and, when endocarditis is present, small doses, intravenously. *Veratrum viride* should be given to reduce the blood-pressure and the friction of the blood column upon the endocardium, if the blood-pressure is high, the patient keeping the recumbent position. Free use of *alkaline waters* is also indicated to facilitate the elimination of detritus.

Quinine, digitalis, and all agents which tend to raise the blood-pressure, including opium, which does so by causing constriction of all arterioles, are contraindicated.

Enuresis, 24. Treatment 733

Many of these cases are in subjects suffering from hypothyroidia; hence the fact that enuresis is frequently observed among backward children, and in those having adenoids, enlarged tonsils, or who are undersized. In all such, *thyroid gland* in small doses, 1/4 to 1/2 grain (0.016 to 0.03 Gm.) three times is very helpful, and sometimes curative, while improving the general health.

Enteritis, Acute. General article 1750

Enteritis, Chronic. General article 1753

Epilepsy. General article.. 20, 1454

Erysipelas. Treatment, 19, 738, 770

The unfavorable results of medical treatment in this disease are probably due to the fact that the cutaneous tissues are ill supplied with antibodies. Hence the fact that good results have been obtained from *thyroid gland*. It should, however, be given in large doses, 2 grains (0.12 Gm.) every three hours, with *hypophysis sicca* ½ grain (0.03 Gm.), to promptly raise the blood-pressure and thus cause more arterial blood to circulate in the peripheral or cutaneous tissues.

Fractures, Delayed Union in. Treatment 710, 1145

Although *thyroid gland* has been recommended by several surgeons to promote the healing process, it should be remembered that it represents but one of the participants in the function, that of catabolism. Hence the disappointment recorded by others. A far better result should be expected from an adjustment of the treatment to the needs of the process, viz., *calcium lactate* 5 grains (0.3 Gm.) and *thymus gland* 5 grains (0.3 Gm.) each in tablet form, *t.i.d.*, with meals, to activate the formation of osseous calcium phosphate; also, *after* each meal, a capsule containing *strychnine* 1/40 grain (0.0016 Gm.) to stimulate the adrenals and promote general oxygenation and metabolism, *hypophysis sicca*, posterior lobe, 1/10 grain (0.006 Gm.), to raise the vascular tone and activate the circulation at the seat of fracture, and *thyroid* 1 grain (0.06 Gm.), to promote with the thymus, calcium metabolism, and the catabolism of wastes.

Gangrene, Gaseous 19

Gastrectasia.

Dilatation of the stomach is commonly due in debilitated people, to atony of the gastric muscularis owing to depressed functional activity of the adrenals, *i.e.*, hypoadrenia. In this particular form, *strychnine* given in increasing doses until 1/20 grain (0.003 Gm.) is administered *t.i.d.*, with *Blaud pill* 2 grains (0.13 Gm.), if the red corpuscle count is low, is often very beneficial. Where the digestion is delayed, *pepsin* 10 grains (0.6 Gm.) with *dilute hydrochloric acid* 15 minutes after meals, in water, not only improves the gastric digestion but also that of the intestinal canal by promoting the secretory activity of the pancreas.

Glycosuria 35, 38

Gout and Gouty Diathesis. General article 1500

Growth, Stunted. Treatment .. 108

Although individual extracts have been credited with growth promoting properties, it is only when the individual happens to lack a given hormone, thryoid in the dwarfism of cretinism or hypothyroidia, for instance, that satisfactory results are obtained. Where, however, as in the vast majority of cases observed in practice, there are no detectable endocrin stigmata to serve as guide, the individual being merely very short for his age though well formed, *all* the endocrins concerned with general metabolism, including that of the skeleton, the main featur in the process, are necessary. For a child of ten years, for instance, the following combination is indicated: *Calcium lactate* 3 grains (0.2 Gm.) and *thymus gland* 3 grains (0.3 Gm.) *t.i.d.*, with meals, to activate the formation of the osseous calcium phosphate, and after each meal, a capsule containing *strychnine* 1/60 grain (0.001 Gm.) to stimulate the adrenals and promote general oxygenation and anabolism; *hypophysis sicca*, posterior lobe, 1/15 grain (0.004 Gm.), to raise the vascular tone and activate the circulation in all tissues concerned with growth, nervous, muscular and osseous, and finally, *thyroid gland* 1/12 grain (0.005 Gm.), to promote the catabolism of wastes. A well balanced diet, including vegetables and sweets, out-of-door life and prolonged night rest, are important features of the process.

Hay Fever or Hyperesthetic Rhinitis. General article 1709

Heart Disorders, 8. Treatment, 8, 755, 758, 764.

The indications for the endocrin products used in heart disorders are similar to those for digitalis and its congeners: when there is hyposystole or ventricular deficiency, *i.e.*, heart failure with dilatation. They are far superior to digitalis, however, in the *heart failure of toxic states*, terminal hypoadrenia, *i.e.*, to exhausted adrenals; in such cases *adrenalin* 10 minims (0.6 c.c.) of the 1 to 1000 solution in a syringeful of saline solution injected intramuscularly twice, in the twenty-four hours often saves life; *hypophysis sicca* $\frac{1}{10}$ grain (0.006 Gm.) given orally, when there is no delirium, and the vascular tension is low, is a powerful adjuvant and serves to keep up the effect of the adrenalin when the latter is stopped. In *tachycardia* due to low vascular tension, including that due to hyperthyroidism, *hypophysis sicca* is also useful in some cases along with remedies calculated to oppose the causative disorder. In pure *atonic dilatation*, with low blood-pressure, the best effects are obtained from *strychnine* $\frac{1}{40}$ grain (0.0016 Gm.), which stimulates the adrenals, and *hypophysis sicca* $\frac{1}{10}$ grain (0.006 Gm.), given together after meals; in some cases the effect is more marked and lasting than when digitalis is used. In *cardiac collapse*, the *liquor hypophysis* of the U. S. P. or *pituitrin*, should be used, 15 minims (0.9 c.c.) being injected intramuscularly. In *valvular disorders*, in which digitalis is indicated, *digitalin* in full doses gives better results than the organic products. Where, however, it tends to derange the stomach, a smaller dose may be given with *strychnine* and *hypophysis sicca* in the doses mentioned above.

Heart, Senile 9

Hemophilia. General article .. 1891

Hemorrhagic Disorders. Treatment 755, 765, 769

Both the adrenal and pituitary extractives possessing the property of stimulating the involuntary or unstriated muscles, they cause constriction of the arterioles or terminal arterioles. By thus reducing their caliber they reduce blood flow, and as is well shown when they are used locally, can completely check it. Hence their value in all forms of hemorrhage. In *uterine hemorrhage* related to parturition, uterine relaxation, post-partum, placenta previa, abortion, etc., the *liquor hypophysis* or *pituitrin* from 8 to 16 minims (0.5 to 1 c.c.) should be injected intramuscularly. In *metrorrhagia* or *menorrhagia* this measure may also be necessary, but if there is no urgency, *hypophysis sicca* in $\frac{1}{4}$-grain (0.016 Gm.) doses every four hours until the excessive flow ceases, then twice daily for a few days, to sustain the effect, will prove efficient. In *hematemesis* 30 minims (1.8 c.c.) of *adrenalin* 1 to 1000 solution in a little water, taken orally immediately after blood has been vomited, and 15 minims (0.90 c.c.) later, in a syringeful of saline solution injected intramuscularly, will usually stop it; if not, *morphine* hypodermically will cause additional constriction of the arterioles and do so. The same procedure is indicated in *hemoptysis* excepting, of course, the oral use of adrenalin. In both *hematemesis* and *hemoptysis*, *pituitary* preparations also stop the hemorrhage but by causing, unlike *adrenalin*, a rise of blood-pressure, they favor recurrence owing to the vast vascular supply of the organs affected. In threatening cases both *morphine* and *adrenalin* may be injected simultaneously in the manner described above. Tincture of *veratrum viride* 6 minims (0.36 c.c.) every three hours, will tend to prevent recurrence by causing relaxation of the large vessels and the splanchnic area. If the heart is weak, however, the patient should be closely watched and periodical injections of *adrenalin* given intramuscularly to sustain it. The veratrum should be stopped when the blood-pressure falls below 100 m.m. In *intestinal hemorrhage* 30 minims (1.8 c.c.) of *adrenalin* 1 to 1000 solution may be given orally every three hours, with *morphine* hypodermically.

Hysteria. Treatment 788, 1380

This common disorder is one of the many which cause me to deplore the fact that the posterior body is now generally believed, *without a single tangible proof*, to be a secreting organ. It causes investigators to neglect it as nerve center—as its older name well indicates "neural lobe," and, therefore, to contribute nothing to progress. Hysteria, from my viewpoint, is due to hyperemia of this lobe—or chief sympathetic ganglion, and containing like all such, the adrenal principle. This hyperemia may be caused or increased by any condition which provokes a marked and frequent rise of the vascular tension: frequently repeated sexual orgasm, chorea, anger, shock, worry, prolonged febrile processes, excessive mental labor, alcoholism, morphinism, etc., and in delicate girls, by autotoxins of intestinal origin, or inadequately broken down wastes.

The general nerve centers, including primarily the posterior lobe of the pituitary, being constantly hyperesthetic, an attack is readily induced by any condition which increases temporarily their hyperemia: excitement, joy, grief, fear, etc., or which submits them to too sudden a concussion: a loud noise, a horrifying sight, a severe pain, etc. The mental, sensory, motor and secretory morbid phenomena witnessed are all due to imperfect co-ordination of the circulation of the organs interested, including those of special sense, when, as is frequently the case, vision, hearing, smell and taste are impaired.

Attacks of *hystero-epilepsy* are but violent exacerbations of the morbid process in which the muscles, the cortex and the spinal motor cells are abnormally hyperemic.

The belief of many that attacks of hysteria are artificial is groundless. Hysterical subjects should be treated as solicitously as epileptics. The treatment should aim to decongest the posterior pituitary. On retiring, *potassium bromide* alternating with *veratrum viride* should be given to depress the vascular center and facilitate ischemia of all cerebral centers during sleep. Occasional *saline purgatives* should be given to keep the bowels free of any products which when absorbed tend to increase the vascular tension. Physical *rest* is necessary to prevent the accumulation of wastes, which do likewise.

During *attacks*, *apomorphine* hypodermically causes relaxation of the arterioles. In severe cases and in hystero-epilepsy, this may be preceded by inhalations of *amyl nitrite* to produce a similar effect promptly. When prolonged these inhalations depress both the sympathetic and vasomotor centers. In all cases *saline solution* hypodermically or, as enema is very useful to increase the fluidity of the blood and inhibit the irritability of all centers.

Idiocy. General articles, 277 to 300. Treatment, according to its various causes, 193, 275, 303, 311.

The *prophylaxis* of idiocy should be adopted as a habit by the medical man, with *all* infants. Besides being on the alert for ductless-gland stigmata, he should urge upon mothers the importance of *breast nursing* as a preventive, and insist upon it if any stigmata appear. If defeated in his efforts, *fresh-drawn milk*, cows' or preferably *goats' milk*, should be ordered, any delay in its use entailing the chemical destruction of nucleins and other substances necessary for the ductless glands. Many of the mental disorders of childhood, including idiocy, would be prevented if in all febrile infectious disorders such as measles, scarlatina, diphtheria, etc., hypodermoclysis, or, at least, *saline solution* per rectum, or as beverage, were employed to promote the fluidity of the blood, enhance osmosis and thus prevent autolysis to which the lesions in the delicate ductless glands are due.

Again, where, as in certain families, there is predilection to idiocy in the offspring, the endocrin stigmata of each parent should be carefully studied, most of the vulnerability to disease transmitted to children being primarily endocrin. This applies to syphilis as well as to other inherited disorders of children. Treatment of the parents in the direction of the stigmata revealed, before and after conception has taken place, including *thyroid* if a syphilitic history, or where hypothyroidia from any cause prevails, can prevent sacrifice of the child's mind. As an example, I may mention a case of my own in which a physically and mentally perfect child was obtained, through appropriate treatment of the pregnant mother, although her first three children had been idiots.

Impotence. Treatment 782

In cases other than those due to an attitude of mind, the so-called "nervous cases," *strychnine* 1/60 grain

(0.001 Gm.), by enhancing oxidation, *thymus* 5 grains (0.3 Gm.), to supply nucleins, and *hypophysis sicca* 1/10 grain (0.006 Gm.) in a capsule. morning and evening, gradually build up the atonic centers. Stellwagon found the *anterior* lobe of *pituitary* 2⅛ to 5 grains (0.14 to 0.3 Gm.) three times a day, with tonics and *prostatic massage* very efficient. *Orchitic extract* 5 grains (0.3 Gm.) *t.i.d.* is also said to be efficient.

Infantile Diarrhea. General article 1742

Infantile Convulsions. 1323, 1324, 1325, 1472.

Like epilepsy, tetanus, eclampsia, etc., infantile convulsions are due to an accumulation of wastes, toxins, etc., in the blood. These poisons by exciting violently the vasomotor center provoke intense hyperemia of the cortex and of the spinal system, the direct cause of the paroxysms. A few whiffs of *amyl nitrite* in teething convulsions suffice to arrest them, in most instances by causing relaxation of the arterioles, with *sweet spirit of nitre* to sustain the effect. A *warm bath* to draw the blood to the surface will deplete the hyperemic centers, particularly if a little mustard is added. In severe cases, *apomorphine* hypodermically or *chloral* by enema. The cause of the convulsions should of course be eliminated if possible.

Infectious Diseases, 18. Treatment, 18, 112, 351.

In all these, as emphasized in the section on *terminal hypoadrenia* (see p. 109), there comes a time when the adrenals, more or less exhausted by the stress laid upon them to sustain the febrile process, fail to contribute enough of their hormone to sustain the cardiovascular tone, and collapse is correspondingly threatened. In all such *adrenalin* 10 minims (0.6 c.c.) of the 1 to 1000 solution in a syringeful of saline solution injected intramuscularly twice in twenty-four hours, frequently prevents fatal collapse.

Influenza 352

Assistant Surgeon General McLaughlin, of the U. S. Public Health Service, said in an address in Boston as late as June 8, 1920, that his purpose was to "review such facts and observations as we possess in the hope that an exposé of our utter helplessness may stimulate further research and give us weapons with which to fight this scourge." Indeed, it is now generally conceded that despite the enormous labor devoted to all subdivisions of influenza, its bacteriology, pathogenesis, pathology and treatment are admittedly in a deplorable state. It was thought after the great pandemic of 1889 and Pfeiffer's labors in 1892 that mastery of the disease was near at hand. The B. influenzæ, however, has increasingly lost its claim to recognition, while filtrable viruses and other uncertain pathogenic agents, promise only so far, a certainty of time consuming labors, many years probably, while the disease is starting anew its destructive work in India and Japan at the present writing, June, 1920.

A comprehensive study of the whole question, including the epidemics of 1889-90 and 1918 and the recent recrudescence, as basis for clinical experience, led me to conclude not only that we had been working on misleading lines, but that the filtrable virus and other pathogenic factors now in course of investigation would prove quite as disappointing. The study referred to was read on March 16, 1920, before the Medical Society of the County of Kings, Brooklyn, and published in the New York Medical Journal of May 15, 1920, to which the reader is referred for details, the purpose of this article being only to review those features of the research, and additional laboratory results obtained since, which will illustrate the need of the prophylactic and therapeutic measures advocated.

The investigations referred to showed that Pfeiffer bacillus was the true pathogenic organism of influenza but that it did not act in accord with Koch's postulates. I found that it was *in the pulmonary alveoli, which present all conditions for the growth of the Pfeiffer bacillus, hemoglobin, oxygen and temperature, that its colonies were developed* precisely as they are in the laboratory, and that these colonies caused therein lesions which led me to identify the disease as a *pulmonary necrotic alveolitis*. That these air vesicles are deeply involved is well shown *post mortem*. Dr. F. P. McNamara, for instance, who described ninety-five autopsies at the U. S. General Hospital No. 6 by Prof. Winternitz, of Yale,[1] wrote: "The most striking picture and one that is *peculiar to this disease* is the hyaline necrosis involving only the terminal bronchioles and alveolar walls." The cyanosis, upon which so many internists lay stress, and so intense in some cases in my service during the 1918 epidemic, as to give the body a bluish black color, point clearly also to an asphyctic condition which widespread destruction of the air vesicles clearly explains.

Further study then showed that we were protected to a degree at first estimated at 60 per cent., and then (in a requested report to the French Government, June 3, 1920) at 80 per cent., after revision of data, by the nasopharyngeal defenses and the ciliated epithelium of the respiratory tract down to the terminal lobules. So perfect is this nasopharyngeal barrier that moderately contaminated air is found completely sterilized after passing through it. This explains the negative results obtained by practically all investigators who have attempted to provoke the disease by injecting B. influenzæ into the nasal cavities. The germs were destroyed by phagocytes (the cytoplasm of which can be found to contain them) and the mucus of the respiratory passages long before they could reach the alveoli, which alone in the whole tract afforded the conditions necessary for their growth.

The strength of this conception is sustained not only by direct and well established evidence recorded by others besides my own, but also by the ease with which it solves many riddles that older conceptions have failed totally to meet. As instances, I might mention the familiar fact that young men between twenty and thirty years are by far the preferred victims. This is readily explained when we take into account their powerful respiratory activity which causes air contaminated with the Pfeiffer bacillus to reach the alveoli rapidly, *i.e.*, before sterilization of the air can have been completed in their respiratory passages. Again, we know that leaving the sick bed too soon is usually followed by another and often fatal attack of the disease. With numerous alveoli as the seat of active colonies, perfect quiet in bed, by insuring slow respiration, enables the expired air to be sterilized. If, conversely, the patient arises too soon, the increased respiratory activity prevents complete sterilization of the expired current and the inspired current thus carries active germs back to many previously unharmed alveoli, thus starting the disease anew—a true autoinfection.

It accounts also for many previously unexplained clinical phenomena, *e.g.*, for the cyanosis, sometimes intense, by the interference with oxygenation of the blood precisely where this process is carried out, the alveoli; also for the early high temperature with relatively low pulse, thus shown not to be a true fever, but the result of a passive dilatation (asphyctic relaxation) of the peripheral arterioles, thus permitting the admission of blood of higher temperature (103° to 105°) from the deeper organs into the cutaneous vessels; also for the typical leucopenia due to the deficient metabolism in the leucocytogenic tissues incident upon the general cyanosis; also for the so-called apyretic cases in which the sensation of cold is due to cyanotic blood; also for the vulnerability to complications, the production of protective antibodies being inhibited by deficient oxygenation of all tissues; also for the formation of methemoglobin, deficient oxygenation of the blood causing the hemoglobin to be so reduced by the tissues as to cause it to break down; also for the occurrence of the various forms, abdominal, nervous, asphyctic, aural, etc., the general vasodilation and inadequate defensive efficiency resulting from deficient oxygenation and metabolism, causing any region predisposed to disease to become the prey of any bacteria it may contain; also for the somnolence suggesting "sleeping sickness," etc., when marked, due to the same asphyctic condition of the brain; also for the intense lassitude and myasthenia persisting long into convalescence due likewise to deficient tissue oxygenation and slowed metabolism; finally, for the short lived immunity conferred on some subjects, the respiratory tract retaining for a short time the exacerbation of defensive activity initiated by the invasion of pathogenic germs.

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[1] McNamara: Boston Med. and Surg. Jour., Feb. 12, 1920.

Prophylaxis.—The foregoing remarks have pointedly indicated where protection against infection is paramount, *i.e.*, the respiratory tract. This is so well established, that, as is well known, antiseptic sprays, gargles, fumes and douches are employed by most clinicians. But is it as antiseptics that they act? The recent war has taught us an important lesson in this connection: It was found that antiseptics, including the newer ones, in solutions sufficiently strong to kill bacteria, also killed tissue cells. In the nasopharyngeal passages, therefore, if antiseptic solutions are too weak they are useless; if strong enough to destroy bacteria they do harm by inhibiting the local protective functions. Other data showed, however, particularly Lambert's experiments, that while *iodine* was very active as a sterilizer in a 1 to 2000 solution, it promoted cellular activity. Pharmacology also teaches that iodine is the specific excitant of lymphoid tissues and therefore of phagocytosis.

It was also observed during the war that in toxic gas manufacturing plants, in which emanations of irritating gases, chlorine, sulphur, dioxide, etc (not phosgene) in hardly perceptible proportions permeated the air, immunity was conferred upon workers therein while influenza reigned unchecked in the neighborhood. Shuffelbotham[2] who investigated this report in twenty different and widely separated districts in England found that workmen actually enjoyed a "very high degree of immunity from infection." A. Gregor[3] ascertained bacteriologically that workers so exposed showed a marked decrease in the pharyngeal flora even twenty-four hours after exposure to the fumes. Tweddell[4] has observed similar protection at the Edgemont Arsenal in this country. Consular reports[5] from Germany had also called attention to the protective influence of evaporating turpentine in workmen during an epidemic.

All the practical phases of the question, clinical, experimental and industrial, unite, therefore, in pointing to the value of measures *which enhance the defensive efficiency of the respiratory tract* as the foundation of our prophylactic measures. Normally, as previously stated, its tissues defend us to the extent perhaps of 80 per cent. It is the *remaining 20 per cent.* of defensive efficiency that we should aim to promote to obtain complete protection. How may we secure it?

We have seen that iodine is superior to any of the antiseptics used because, while provoking a local defensive reaction, it favored the vital activity of the lymphoid and epithelial cells. Yet it must be employed with due care, as shown below.

Luckhardt, Hoch, Schroeder and Weiland[6] have recently emphasized the dangers attending the direct application of iodine fumes obtained from crystals by heat as recommended by some authors for the treatment of diseases of the respiratory tract. This corresponds precisely with my own experience. Personal tests showed that even as weak a solution of iodine as 1 to 2000 caused too much smarting when sprayed into the nasal cavities to be employed, but that when iodine crystals were slowly converted into fumes by the heat of a small alcohol lamp 15 centimeters below them, and mixed with air in the proportion of 0.33 grams of crystals to 15 cubic metres of air (the size of a very small room used as inhalatorium) the *iodized air* could be inhaled comfortably. Any stronger dilution caused a symptom which indicates that the proportion of iodine is too great, viz., *persistent smarting of the conjunctiva* after the first slight pricking sensation experienced on entering the iodized air chamber. This affords a delicate test for the adjustment of the mixture to proper proportions by the admission of additional air into the room.

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[2] Shuffelbotham: Brit. Med. Jour., Apr. 19, 1919.

[3] A. Gregor: Brit. Med. Jour., Oct. 25, 1919.

[4] Tweddell: Letter to Med. Rec., Jan. 24, 1920.

[5] U. S. Consular Reports: Amer. Med., Apr., 1905.

[6] Luckhardt, Koch, Schroeder, and Weiland: Jour. of Pharmacol., Mar., 1920.

The duration of the slight pungency experienced in the upper respiratory tract, beginning with a sensation of dryness and followed by a freer flow of mucus, *obtained with 5 grains of* crystals, was about one hour. *It was found*, however, that these effects could be perpetuated indefinitely by dropping tincture of iodine upon the small receptacle over the alcohol flame which had held the crystals, at the rate of four drops a minute, *i.e.*, one-half ounce an hour. The fumes thus formed were inhaled hour after hour without difficulty or causing irritation, although starch held over the heated iodine tincture, showed distinctly by turning blue that the halogen was being vaporized, while the odor of the air of the inhalatorium to those entering from the outside was characteristic.

The effects of a stay of but three hours in the inhalatorium so charged were unexpectedly prolonged. Although no deep breaths had been taken, the odor of iodine *per se* (different somewhat from that of the tincture itself) was perceptible the whole of the following day off and on, that is to say, about thirty-two hours. This accounts for the fact that Gregor[7] had found that the nasopharyngeal organisms of the workmen exposed to chlorine and other fumes were markedly decreased as much as 24 hours after leaving their plants. When we consider the superiority of iodine fumes over those to which they were exposed, and also the relative vulnerability of the B. influenzæ, there is every reason to believe that three hours of exposure to iodine fumes under the conditions mentioned would afford at least protection for an additional five hours, during an epidemic, by enhancing the defensive efficiency of the whole respiratory tract.

The practical bearing of these observations is that *all public places*, schools, places of amusement, shops, hotels, churches, offices, factories, barracks, hospitals, etc., where many people spend much time, either as pupils, employees, visitors, etc., and which are now foci of infection, could be converted into as many *sterilizing and immunizing inhalatoria* provided the air in them be kept iodized in the proportion above mentioned, by multiplying as needed and distributing evenly throughout the area to be iodized, what apparatus—very simple and inexpensive as we shall see—may be needed for that area. Or, better, where a suitably situated adjoining room is available, fresh air from an open window may be strongly iodized, and driven by a turbine or rotatory fans through an enclosed shaft to the occupied room, and in such proportions as to insure the dilution specified. The iodized air can thus be kept pure, escape vents being supplied through lowered upper sashes or transoms for the escape of the air from the occupied quarters.

During the hours all such places would be used, all those exposed to the iodized air three hours would, estimating very conservatively, be protected five hours besides, thus aggregating eight hours, at least until bed time. If the subjects happen to spend the evening in a place of amusement, church, etc., or any other sterilizing inhalatoria, the protection would extend to the following morning. Yet, absolute safety imposes the need of an iodized air apparatus *in every home*, thus perpetuating its effects throughout the twenty-four hours.

To provide for out-of-door workers, laborers, masons, bricklayers, drivers, street venders, etc., *sterilizing tents* might be provided, but here again the need of an apparatus at home imposes itself, since workers would hardly consent to spend the time necessary during the day, even to protect themselves. Indeed, the more the question is studied the more it becomes plain that all residences, great and small, the palace down to the hovel, should, if legally possible, be made by the municipal authorities and under their watchful eyes, to be kept iodized, and if possible, at the expense of the commonwealth, to insure execution. This alone would cause complete protection.

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[7] Gregor: *Loc. cit.*

The cost of adequate protection can be made comparatively slight if it is realized that expensive apparatus is quite unnecessary. Among the poor whose living quarters are small, what lighting, heating or cooking facilities they possess may be utilized with the aid of slight ingenuity. Or a small open box—a 100-cigar box,—for instance—may be used, by removing one of its ends and replacing the latter by a piece of wire netting. This netting is used, the box standing on its other end, to support a small metallic cover or saucer, in which are placed the iodine crystals. These, in turn,—or the drops of tincture of iodine—are gradually evaporated by the flame of a small alcohol lamp placed on the floor of the upright box, the three walls of which prevent side draughts from disturbing the flame, while forming a chamber of warmed air which propels the iodine upward and disseminates them. The same box can be used for the evaporation of the tincture of iodine drops, by nailing to it an elbow support for a glass funnel the beak of which contains a stopper provided with a small hole, so regulated as to allow the tincture of iodine it holds to drop on the evaporating plate as needed.

Where such comprehensive measures cannot be carried out, a *small inhaler* calculated to permit the inhalation of *cold* iodine emanations, which are far less dense than the fumes evolved by heat, can be used. It consists merely of a glass tube one end of which is enlarged into a bulb calculated to fit into either nostril. Each end is packed, though not tightly, with a wad of cotton wool, 3 grains (0.2 Gm.) of iodine crystals being placed between the two wads, *i.e.*, in the middle of the inhaler. One end of the latter being enlarged and bulb shaped, the bulb is introduced into each nostril in turn. On inhaling slowly but steadily through it, the iodine emanation will be felt to penetrate far down. To insure filling the entire bronchial tree down to the alveoli, after removing the inhaler, the nose is closed with the fingers, and efforts to blow the iodine out through the nose, the mouth being shut, are made. The slight warmth and pricking sensation experienced in the nose and throat disappears in a few minutes. Not more than two inhalations from the inhaler should be taken. These suffice, after clearing the nose to excite a defensive reaction which may be sustained if the procedure is repeated several times a day. Various pocket inhalers available in the shops may be used for the same purpose, but in an emergency, I found that discarded vaccine tubes served the purpose very well.

Such an inhaler is particularly useful where the air is likely to be contaminated, in tramways, places of amusement, shops, etc. As stated elsewhere,[8] it should be used before leaving home and every three hours to keep the nasal mucosa on the defensive. At present, coughing and sneezing individuals are urged to cover their faces, nose, and mouth with their handkerchiefs; but everyone exposed should likewise protect himself with his handkerchief. A small inhaler hidden in it and used materially reduces the danger of infection. A few whiffs suffice. Again, many bacteria inhaled are present at first in the anterior nasal cavities; if the inhaler is used again on reaching home, and the nose freely blown, additional protection is afforded. Although the January-February (1920) epidemic afforded ground for the belief that this measure affords protection, thousands of cases can alone determine its value. *A priori*, however, it is obvious that the general public measures advocated in the foregoing pages, offer a far greater opportunity for adequate protection than the desultory use of any inhaler.

Oil of turpentine, though far less efficient than iodine, might prove useful in the absence of the latter. It may be used in the same three ways, but its odor is unpleasant to most people. *Terebene, terpene hydrate* and *pine needle oil* are more pleasant but also more expensive and less efficient than iodine. All are also evaporated by heat, but they should be floated on heated water. Public places, homes, vehicles, etc., may be used as inhalatoria, as in Europe, their atmosphere being heavily loaded with one or several essential oils. *Oil of eucalyptus* is also useful but not as active a stimulant of the respiratory mucosa. One-half each of the *oils of turpentine* and *eucalyptol*, dropped on the cotton of a pocket inhaler, used frequently during the day, are stimulating to the respiratory passages but not to the same degree as iodine.

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[8] Sajous: New York Med. Jour., May 15, 1920, p. 842.

In hospitals, respirators on the Yeo principle could be used with *terebene* as excitant, the continuous use and close proximity to the respiratory tract requiring a less irritating agent. Or, if the mask be used it may be dropped on it opposite the nostrils.

The *masks* used in the United States during the 1918 epidemic, even those made of four-ply gauze, were defective in that they allowed germs deposited on their surface, and when dried, to be drawn into the nasal cavities, with the inspired air. A bit of snuff placed on the mask opposite the nostrils, when in position, or work where coal dust permeates the air, will soon illustrate this fact, when the wearer is subjected to exertion. Again, the stifling caused by four-ply gauze against the nostrils causes the mask to be removed, often without pretext, particularly by nurses.

Study of this whole question showed that these drawbacks could be avoided by means of a newer model: a boat-like hood made of canvas which covers the nose and mouth, though not in contact with them, each side being extended by flaps made of the same material and provided with tapes for attachment behind the head. The wearer breathes without discomfort, the air circulating in and out from the side only. The boat-like hood covering the nose and mouth being absolutely impermeable, it prevents all access to the nose or throat of bacteria-laden droplets even if they are coughed directly into the face. The few striking the sides having to travel a circuitous route cannot reach the nasal cavities, even aided by the inspiratory suction, with sufficient velocity to reach beyond the nasopharyngeal barriers, where they would be promptly destroyed, long before, therefore, having reached even the bronchial tract.

Important in this connection is the fact that the velocity with which contaminated air is inhaled determines whether infection will occur or not. The great prevalence of the disease among young men, as we have seen, is explained by their great chest vigor. Hence the danger of any violent exertion during an epidemic, dancing, skating, drilling (as personally observed in my own command) and other sources of unusual activity, the aim being to prevent the B. influenzæ from reaching the alveoli.

Cold quarters, apartments, rooms, etc., favor infecting by lowering the activity of the defensive ferments of the respiratory tract. Living quarters should not be allowed to reach below 65° F. during an epidemic though well ventilated.

Treatment.—Anyone showing a rise of temperature and other symptoms of influenza during an epidemic should at once be kept in bed, isolated, reported, and the room at least, placarded. Agar plates and smears of the nasopharyngeal mucus should then determine the presence or absence of disease. In the meantime, a light *calomel purge*, 1 grain (0.06 Gm.) in divided doses, followed by a mild *saline aperient*, should be given. I have pointed out[9] that mercury is probably our most energetic stimulant of defensive function.

The room, preferably a small one, should be iodized (though not sufficiently so to prove irritating to the eyes) with *iodine fumes* generated near the patient's bed. The aim should be *to check the formation of colonies in the alveoli* and *to destroy the influenza bacilli in the respiratory tract at the earliest possible moment*, the bacilli from the alveolar colonies serving to infect other alveoli. The iodine fumes would also protect the nurse as they readily penetrate the sides of the mask. The latter should always be worn by her in the patient's room, not only to protect her but also to prevent her becoming a carrier. The newer mask described above contains, on its facial side, a small pocket into which absorbent cotton may be placed, to hold a few drops of eucalyptus oil thus affording further protection.

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[9] Present volume, p. 1147.

A *bed-tent*, the upper part of which would reach above a window, with the upper sash of which would be somewhat lowered, would serve to concentrate the fumes in a small area and increase their efficiency. The patient, however, should be kept warm, though well supplied with fresh air. The small inhaling tube can be used if the air cannot be iodized satisfactorily.

In children, in whom the iodine inhaler cannot be used, steam inhalations composed of *menthol* ½ dram (2 Gm.), and *fluid extract of eucalyptus* 2 ounces (60 Gm.), one teaspoonful to a pint (500 c.c.) of hot water, are efficient, being both stimulating and antiseptic, but not sufficiently so to harm the tissues. The ubiquitous sweet spirit of niter should not be used, all nitrites serving to dilate the arterioles, thus aggravating one of the evil effects of the disease, that to which the cyanosis is partly due.

Conversely, the *salicylates* have wrongly been abandoned on the plea that they caused cyanosis—a criticism which applied only to excessive doses—whereas this symptom, we have seen, is due to the disease itself. In 1907[10] I urged that in small therapeutic doses the salicylates caused constriction of the arterioles and reduced the volume of blood supplied to all tissues including the painful areas. It is precisely through this action that they reduce the so-called "fever" of influenza, which is not a true fever, but the result of flooding of the cutaneous capillaries resulting from the influenzal dilatation of these arterioles. They also relieve by the same process, the racking headache and the so-called temperature, the myalgia and other characteristic discomforts, by causing the capillaries to resume more or less their normal caliber. This applies to all organs, which are the seat, as necropsies show, of marked congestion, including particularly those that suffer most, the lungs (assailed directly by the B. influenzæ in their alveoli and indirectly by the passive congestion of their immense capillary system) and also the adrenals. Indeed, interpreted in the light of my views, it would be difficult to find a more perfect specific than the salicylates. An essential feature of these agents, however, is that they should be used in *small doses*, since large doses by exaggerating the constriction of the arterioles, produce asphyctic effects on the tissues resembling those due to influenza.

The *ammonium salicylate* is the best salt to use since it tends also to reduce the acidosis; 10 grains (0.6 Gm.) at one dose, followed by 5 grains (0.3 Gm.) every two hours, has given me the best results. Or, *salicin*, in 10-grain (0.6 Gm.) doses every hour, four times, then every two hours, is equally helpful. The reduction of the so-called "fever" is promptly effected and the suffering is controlled even more rapidly by injecting intravenously, but slowly 5 to 7 grains (0.3 to 0.45 Gm.) of *sodium salicylate* dissolved in 30 minims (1.8 c.c.) of sterile water, twice in the twenty-four hours.

Of the coal-tars, which have the same effect on the arterioles but are more fleeting, antipyrin and acetanilid are treacherous, acting well, perhaps, for a while, then suddenly even in small doses, causing at times threatening cardiac depression.

Acetphenetidin 5 grains (0.3 Gm.), with *sodium bicarbonate* 10 grains (0.6 Gm.), every three hours, does not seem to possess these defects and is very helpful when the salicylates cannot be obtained. *Heroin*, which includes peripheral vasoconstriction among its effects, is useful when the suffering, including the dyspnea and edema, resists the foregoing agents.

When the circulatory equilibrium has been re-established by the use of the salicylates or their congeners, *i.e.*, when the peripheral hyperemia or so-called fever has abated, thus indicating that the adrenals are no longer the seat of paretic passive congestion, *strychnine* which, as I urged in 1903 and 1907, and recently confirmed by Stewart and Rogoff, stimulates the adrenals, should be used to keep the arterioles contracted, a function of these organs. One of my pupils and former laboratory assistants, Dr. V. P. Jourdan, of Bristol, Pa., found in a series of 750 cases, including 46 with marked pulmonary complications, and a total mortality of but 8 cases, that small doses were futile (a logical conclusion in view of the torpor of all centers due to the general asphyctic trend) and that 1/30-grain (0.002 Gm.) doses increased to 1/20 grain (0.003 Gm.) four times a day, or 1/15 grain (0.004 Gm.) twice daily, were necessary to obtain good results. When pulmonary edema is present, strychnine is contraindicated, the resulting rise of blood-pressure tending to aggravate it.

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[10] See this volume, p. 1282.

The adrenal insufficiency upon which French clinicians first laid considerable stress and which several American internists have confirmed repeatedly, has led to the use of *adrenalin*—in most instances with excellent results, but in a few with no benefit. Its use, 10 to 15 minims (0.6 to 0.9 c.c.) of the 1 to 1000 solution in 30 minims (1.8 c.c.) of saline solution, injected slowly intramuscularly, is subject to the same rule as strychnine insofar as peripheral hyperthermia ("fever") is concerned, when it should not be used, but it does not tend with the small doses employed, like strychnine, to increase pulmonary edema, and may then be helpful.

An auxiliary measure of material help in these cases, and calculated to offset both the marked acidosis and also the viscidity of the blood, is a pleasant beverage composed of one-half each of *milk* and *saline solution* and 1 dram (4 Gm.) of *sodium bicarbonate* to the pint (500 c.c.). One tumblerful every four hours, besides promoting general osmosis, insures free renal action, thus facilitating the elimination of toxic wastes. Rectal injections of warm saline solution are preferable to cathartics to keep the bowels open.

No patient should be allowed to leave his bed until agar plates and smears of his nasopharyngeal and tracheal mucus demonstrate that no active colonies exist in his alveoli. This same precaution is suggested for the examination of possible carriers from infected districts for the protection of municipalities.

Intestinal Paresis. Treatment. 772

In the arrest of intestinal peristalsis following operations, the *liquor hypophysis* U. S. P or *pituitrin* in 15-minim (0.90 c.c.) doses injected intramuscularly, repeated in one hour if necessary, sometimes proves very efficient. It has replaced all other organic preparations used for the same purpose, owing to its greater safety. An *extract of bile* in 5- to 15- grain (0.3 to 1 Gm.) doses and the *sodium taurocholate* in 1/2- to 3- grain (0.03 to 0.2 Gm.) doses have also been recommended.

Jaundice, Malignant 347

Lactation, Deficient. Treatment. 780

While *mammary gland* has been recommended by some and found valueless by others to increase the flow of milk, *hypophysis sicca* or *pituitrin* (posterior lobe) in 1/10- or 1/4- grain (0.006 or 0.016 Gm.) doses *t.i.d.*, has been, on the whole, generally commended.

Leprosy. Treatment 735

The aim should be to destroy the bacillus lepræ by increasing the aggressive power of the phagocytes and the bacteriolytic activity of the blood. *Thyroid gland* 2 grains (0.13 Gm.) *t.i.d.* (in adults), to increase the thyroiodase (opsonin) replaced, after one week, by *iodide of mercury* 1/16 grain (0.004 Gm.) also *t.i.d.*, reducing the dose slightly if salivation appears. At least one quart (liter) of some *saline mineral water* daily to preserve the fluidity of the blood and thus insure the free penetration of the bacteriolytic plasma into all capillaries and neuro-fibrils, and the prompt elimination of the increased wastes. The diet should include a free supply of *vegetables and fruit* to provide the blood with alkaline salts.

Leucorrhea 25

Leukemia.

To increase the blood's proteolytic activity, *thyroid gland* 2 grains (0.13 Gm.) *t.i.d.*, in adults, with *oxygen inhalations*, or systematic daily courses of *deep breathing* in the open air. After one week, *saline solution* intravenously, six ounces being injected slowly every other day. The *free use* of *alkaline waters* to facilitate the elimination of detritus by the intestinal and urinary systems, is also indicated.

Lupus. Treatment 735

Painting the edges of the ulcer daily with a 75 per cent. solution of *acetic acid* followed by rinsing with water, and *thyroid gland* 2 grains (0.13 Gm.) *t.i.d.*, sometimes gives excellent results when the diseased area is small.

Measles 19

Meningitis 20

Menopause. Treatment, 710, 777, 779, 1145, 1168.

In physiological or surgical menopause, *corpus luteum* 3 grains (0.2 Gm.), *thyroid gland* 1 grain (0.065 Gm.) and *hypophysis sicca* $\frac{1}{10}$ grain (0.006 Gm.) in one capsule after meals, give better results than either *ovarian gland* or *corpus luteum* alone, even when given in much larger doses. The cessation of the menstrual function entails an accumulation of wastes, the destruction of which incites periodical exacerbations of endocrin activity, of which the periodical flushes are a sign. By giving the above combination, the autolysis of the wastes is enhanced and the abnormal phenomena are prevented.

Mental Diseases.

● The endocrins, owing to their fundamental participation in both phases of metabolism, *i.e.*, anabolism and catabolism, and in the defensive processes, are of paramount importance in these diseases, when any functional disorder, metabolic or toxic, prevails in addition to the psychogenic. The classification adopted here is that formerly utilized, owing to its clearer adaptation to my purpose. The symptomatic treatment is of course not considered, my aim being only to illustrate the fundamental features connected directly with the endocrins.

INSANITY DUE TO HYPOENDOCRINIA AND A RESULTING TOXEMIA.—This condition, which may be illustrated by forms which are now, such as *puerperal insanity*, generally attributed to a toxemia. From my viewpoint, it occurs as a result of exhaustion of the endocrins during, and as a result of, pregnancy, the glands being originally insufficient to meet the high tide of toxic wastes. As a result, the latter are imperfectly catabolized, and intermediate wastes being toxic, they awaken the mental disorder. The main glands exhausted in these cases being the adrenals and thyroid, we should give first *thyroid gland* 2 grains (0.13 Gm.) *t.i.d.*, to activate catabolism of the wastes, and *adrenalin* 10 minims (0.6 c.c.) of the 1 to 1000 solution in a syringeful of saline solution intramuscularly once daily, to activate oxygenation and general metabolism. Also *warm saline solution enemas* every other night, to promote free alvine and renal elimination. If the case is not of sufficiently long standing to have caused organic lesions in the cortical cells, favorable results may be obtained.

The second form is *uremic insanity*, obviously due to and is generally attributed to a retention of toxic materials which the kidneys should have eliminated. From my viewpoint we have seen, the so-called internal secretion of the kidney is mainly composed of the adrenal dynamic rests that the parenchyma contains (which give the chromaffin test) so that if we inject *adrenalin*, as above, we excite their activity. Small doses of *thyroid gland* $\frac{1}{4}$ grain (0.016 Gm.) *t.i.d.*, to favor the catabolism of wastes, a *salt-free diet* and the *avoidance of meats and eggs* until the mental state is normal, are then indicated. *Adrenal gland* or *nephritin* may then be used to keep the kidneys active dynamically.

Melancholia is another disorder in which endocrin deficiency prevails. In some cases, in fact, the stigmata of hypothyroidia are evident: a dry and harsh skin, often pale and dirty yellow, accompanied usually by signs of hypoadrenia, general vasodilation, sluggish circulation and respiratory torpor.

That wastes are imperfectly catabolized in such cases is self-evident yet, wastes not being actively produced, slow metabolism is the probable direct cause of the depressive state. In cases that are not of too long standing good results are obtained by means of a reconstructive treatment, when the intestinal and renal functions are normally performed, including *thyroid gland* 1 grain (0.065 Gm.), *hypophysis sicca* $\frac{1}{10}$ grain (0.006 Gm.), *strychnine* $\frac{1}{60}$ grain (0.001 Gm.), and *thymus* 2 grains (0.13 Gm.), in a capsule to be taken three times a day, thus enhancing general oxygenation, anabolism, and catabolism, nucleins being provided through the thymus gland.

Menopause insanity is another type due to hypoendocrinia, but special in the sense that its origin is localized. The ovaries having ceased to functionate, they no longer add periodically the unused dynamic constituent of their internal secretion to the general body asset, and being composed (as biochemical tests show) of nucleins and locally formed chromaffin substance (similar to adrenal secretion), general metabolism and the antitoxic properties of the body fluids are slowed in consequence. There is, therefore, besides accumulation of toxics, vasodilation of the arterioles, which the adrenal principle in a measure controls normally. Hence the cerebral hyperemia and the organic changes resulting therefrom if this congestion and the toxemia are allowed to proceed. Hence the value of *ovarian gland* or *corpus luteum*; but their activity is enhanced if simultaneously *suprarenal gland* 2 grains (0.13 Gm.) are given to increase the asset of adrenal hormone and *strychnine*, to stimulate the adrenals themselves, with *thyroid gland* ½ grain (0.03 Gm.) *t.i.d.*, to promote the catabolism of wastes. The gastro-intestinal musculature is often present resulting in gastro-enteroptosis, but the strychnine and suprarenal gland, administered often, corrects this condition if it is not too pronounced.

Insanity Due to Hypoendocrinia Solely.—Typical of this type is *lactational insanity*. In this condition, curiously enough, we are again dealing with deficient adrenal hormone in the sense that, as we have seen, milk contains it. When, therefore, the adrenals after passing through the exhausting period of gestation, are subjected to continued drain through lactation and fail to supply the needs of both maternal milk and vascular system, depression and melancholia occur. This accounts for the fact that this form of insanity may appear both soon or late in the lactational period, its occurrence depending upon the resisting powers of the adrenals. Hence the value, after stopping nursing, of intramuscular injections of *adrenalin* 10 drops of the 1 to 1000 solution daily at first, then less often, with *suprarenal gland* 2 grains (0.13 Gm.), and *hypophysis sicca*, posterior lobe, ⅒ grain (0.006 Gm.), with *reduced iron* ½ grain (0.03 Gm.) in capsule *t.i.d.*, after meals, with *good food* and *out-of-door life*. Strychnine should be avoided, as the adrenals already exhausted, would be further harmed by undue stimulation.

General paresis is essentially the expression of a general collapse of the endocrins, leading to a corresponding break down of the whole organism. Syphilis is an undoubted factor in many cases, Noguchi, in fact, having discovered spirochetæ in the brains of subjects who had died of the disease. But syphilis is but one of the many depressing influences which steadily weaken the functional efficiency of the ductless glands.

In the treatment of general paralysis the misuse of organotherapy may be very harmful. Large doses of *thyroid gland* simply hasten the morbid process. Small doses, on the other hand, not more than 1 grain (0.065 Gm.) thrice daily, counteract it by inciting metabolism. As all other ductless glands are functionally defective, all the ductless glands should be given: *adrenal gland*, *hypophysis sicca*, *thymus* with *ovary* or *corpus luteum* in females, or *testicular* or *orchitic* extract in males. *Good food* and *out-of-door life*, with cessation of all bad habits, will do much for these cases. In some an underlying autointoxication of intestinal origin demands the weekly use of *calomel*, and intestinal antiseptics, *salol*, *creosote carbonate*, or *menthol*.

Senile Dementia.—The treatment on organotherapeutic lines for *general paresis* given above should be tried faithfully here. Senile decay is essentially due to deficient activity of the ductless glands. But coprostasis and other sources of auto-intoxication are omnipresent in the aged. This feature should also receive attention, *purgatives* and *enemas* being used.

Circular Insanity.—This disease, in which mania and melancholia alternate, is also due to some toxemia. During the *maniacal phase*, exaggerated activity of the ductless glands (vide infra), while during the *melancholic phase*, exhaustion of the endocrins by the stress to which they were subjected. The treatment is that indicated for mania, followed after elimination of the cause, by that for melancholia.

INSANITY DUE TO HYPERENDOCRINIA.—*Mania* is an expression of this condition, an exaggerated activity of the endocrins, the purpose of which is to break down either toxins derived from some infectious focus, intestinal, tonsillar, dental, etc., or toxic waste products, including such as are produced during anger or other mental stresses, defective gastro-intestinal digestion, etc. The abnormal exaltation of mental activity, hallucination, etc., is therefore the expression of exaggerated metabolic activity and hyperemia in the cerebral cortex. *Recurrent mania* indicates the presence of a tidal wave of pathogenic toxics or toxins and lasts until these have been broken down by the defensive hormones.

Careful *search for* any *source of intoxication* (teeth, intestines, etc.) or infection (tonsils, nasal cavities, vagina, etc.) should be made. The intestinal canal should be kept free by *frequent purgation*. When the attacks are about due, *saline solution* by the rectum or subcutaneously should be tried. Where any gastric disorder is present, *gastric lavage* is indicated. In *recurrent mania* small doses of *thyroid gland* 1 grain (0.065 Gm.) *t.i.d.*, during the quiescent period, in addition to the foregoing measures, tend to prevent the attacks.

Dementia Precox.—This dread disease which sends 30,000 children to insane asylums each year, and which represents 53 per cent. of our asylum inmates, will be mastered when its relationship with the endocrins will be duly recognized. Cures are beginning to appear when to the inherited predisposition is added a toxemia of focal origin capable of initiating the disease.

In the *catatonic type*, some cause of toxemia whether of intestinal, tonsillar, dental, nasal, uterine, etc., origin, provokes overactivity of the thyroid. From my viewpoint, the excess of secretion which, as is well known, rapidly breaks down fats, likewise breaks down the phosphorized fats of the brain cells, among others, and thus creates the disease. The indication, therefore, is to eliminate the focal infection whatever it be. It is not infrequently located in the cecum, and is revealed by a barium meal X-ray examination. If *colonic flushing*, the fluid being retained at least twenty minutes with the patient lying on his right side, given every other day on retiring, fails to clear the coprostasis, a *cecotomy*, to provide an opening for its efficient accomplishment, is necessary. Simultaneously, the patient should be fed on a *diet rich in fats* and *lecithin*, to build up the myelin of the nerve cells. Organotherapy only increases the severity of the symptoms in the catatonic type.

The *hebephrenic type* (which is placed here only to differentiate it clearly from the former) is also due to a toxemia but with inability of the endocrins to convert the pathogenic toxics or toxins into eliminable end products. These cases sometimes do well by giving them *thymus* 1 grain (0.065 Gm.), *thyroid gland* 1 grain (0.065 Gm.), and *hypophysis sicca* $1/10$ grain (0.006 Gm.), in one capsule after meals, in addition to the measures recommended for the catatonic type. This combination, by enhancing the systemic defensive functions, rids the organism of wastes which probably initiate the disorder in predisposed subjects by exciting the vasomotor center, thus causing hyperemia of the cerebral neurons. While these cases usually show a high blood-pressure for the age of the patient, the reverse is the case in the catatonic type. In both types, these remedial measures only prove efficient, of course, before structural lesions of the brain cells have developed.

The *paranoid type* of dementia precox includes features of both forms symptomatically, but insofar as pathogenesis and treatment are concerned, the measures indicated for the hebephrenic gave the best results. In a personal case the elimination of oxyuris vermicularis (seat worms) was followed by marked improvement.

Consecutive Dementia.—This terminal disorder following an acute mania in which the psychical processes are so inhibited that the patient is hardly more than a living automaton, illustrates the destructive influence on phosphorized fats of the cortical cells of the thyroid, when driven to excessive activity by toxic wastes. It is the result of an active autolysis, with death as only relief.

Metrorrhagia 23

Migraine. General article, 24, 1522

Myocarditis 345

Nephritis 15

Neuralgia. General article ... 1522

Neurasthenia. Treatment, 710, 773, 778, 782, 1175, 1222, 1224, 1231, 1245, 1246, 1258; and **Myasthenia,** Treatment, 710, 773.

The recent experimental demonstration of the correctness of my conclusion in 1903 that it was by stimulating the adrenals that *strychnine* proved so effective in these disorders when organic lesions do not prevail, points to the important rôle played by the endocrins in this disorder. But here, again, the curative process is favored if, with strychnine, small doses of *thyroid*, not more than ½ grain (0.03 Gm.) and *hypophysis sicca* 1/10 grain (0.006 Gm.) are given, not only to enhance metabolic activity, but to raise promptly the vascular tension and thus promote circulatory activity in the nerves and muscles. Where sexual excesses or masturbation underlie the morbid process, *orchitic extract* 2 grains (0.13 Gm.) may replace the hypophysis.

Neuritis. General article 152

Obesity 1145

In the treatment of this condition, considerable circumspection is necessary. Its cause must be definitely ascertained and treated primarily. It is only in cases of low metabolic activity that *thyroid gland* is indicated, and in which hypothyroidia is probable. In such 1 grain (0.065 Gm.) *t.i.d.*, with gradually increased *exercise* and material *reduction of the carbohydrates*, compensated for by meat if the patient partakes of but little of the latter, sometimes gives good results. In some cases, the peripheral arterioles are dilated and torpor of the circulation, aided, perhaps, by a fatty heart, promotes the deposition of adipose tissue. In such, *suprarenal gland* 2 grains (0.13 Gm.) and *ergotin* 1 grain (0.065 Gm.), given with thyroid to constrict the arterioles, antagonize the process. Where the heart is normal *hypophysis sicca* may replace the suprarenal gland, that on the market being seldom reliable.

Pancreatitis 348

Paralysis Agitans. Treatment, 747, 782, 1223, 1324, 1325.

Although Berkley and others have obtained good results from *parathyroid gland*, at least an equal number, including myself, have not noted beneficial effects. Doubtless it is because its preparations degenerate rapidly. *Thyroid gland* ½ grain (0.03 Gm.) and *hypophysis sicca* 1/10 grain (0.006 Gm.) afforded some benefit, but it was only temporarily. *Orchitic extract* 2 grains (0.13 Gm.) three times a day, also afforded but temporary benefit.

Pericarditis 35

Peritonitis 35

Pertussis. General article 1710

Plague. General article 1807

Pleurisy 35, 340

Pneumonia 12

Pneumonia, Senile 12

This form which Osler characterized as "almost the natural end of old people, is not, from my viewpoint, similar to the classic form of lobar pneumonia. It is primarily due to failure of the adrenals which, in the aged, are far less resistant than during youth or middle life (see plate opposite page 88) and yield almost at once to the pneumococcic infection. Hence the term "terminal pneumococcic pneumonia" which has seemed to me to best identify it. As is well known, this senile form may drop upon an aged subject suddenly in the midst of his daily occupations and as suddenly prove fatal. Where, as in most cases, it develops gradually, there may be slight fever, a very moderate rise of blood-pressure, perhaps a chilly sensation, but little if any cough, and no pain in the chest. Then occurs more or less suddenly a rapid lowering of the arterial tension, extreme asthenia, lividity and dilatation of the right heart—all signs of adrenal failure, with pulmonary edema and sometimes adrenal hemorrhage—sudden abdominal pain—as prelethal phenomena.

The usual treatment for lobar pneumonia is futile in these cases. They need repeated doses, 10 minims (0.6 c.c.) of *adrenalin* 1 to 1000 solution in a syringeful of saline solution being injected slowly subcutaneously, carefully avoiding a vein, every two hours three times, then when the heart action and the blood-pressure have improved, four times a day. Perpetuation of the good effects is sometimes better insured by injecting 5 minims (0.3 c.c.) of *liquor hypophysis* or *pituitrin* at a dose, or 15 minims (0.9 c.c.) of either of the two latter, if the blood-pressure is very low. The oral use of these agents, in addition, is often helpful.

The patient's defensive resources being deficient through senile inefficiency of his ductless glands, the use of *antipneumococcus serum* is indicated to increase the bactericidal properties of the body fluids directly, rather than vaccines which do so indirectly and may fail in these cases to provoke a response as antigens. *Sustaining food* in small quantities, frequently repeated, and *creosote carbonate* to prevent tympanities are other indications of importance to which should be added the absolute *avoidance of depressants, particularly the opiates* which are harmful in the aged.

Prurigo.

This cutaneous disorder, so troublesome owing to the pruritus which attends it, is sometimes arrested by *thyroid gland* 2 grains (0.13 Gm.) *t.i.d.*, two days, then 1 grain (0.065 Gm.) *t.i.d.* It is doubtless due to toxic waste products. When the disorder is the result, as is often the case, of poor food, it will only disappear if this cause is eliminated, since by impairing metabolic activity, it inhibits adequate catabolism of wastes.

Psoriasis.

While organotherapy has not given, on the whole, satisfactory results, these were clearly due to the fact that excessive doses were employed. Large doses of *thyroid gland*, for instance, by promoting excessive catabolism, could only aggravate the trouble by adding wastes to those causing the disorder. Not more than 1 grain (0.065 Gm.) *t.i.d.*, should be given. Again, it will prove useless unless marked *reduction of the proteins* which furnish pathogenic wastes is not insisted upon; in some cases, in fact, a strict *vegetarian diet* is necessary to obtain lasting results.

Puerperal Eclampsia. General article 1473

Pulmonary Tuberculosis. General article 1609

Purpura 19

Rabies. General article 1486

Rheumatism, Chronic, 25, 1145, 1168, 1282, 1289, 1293.

The value of *potassium iodide* in this disease, besides elimination of its cause, has caused the use by some of thyroid gland, but the possibility of cardiac complications in the disease, renders the iodides safer.

Scarlatina 19

Scleroderma. Treatment 735

The probable nervous origin of scleroderma and the permanent character of the lesions would seem to render any treatment futile. Yet, *thyroid gland* has been found beneficial by some and useless by others.

Septicemia, Septic Diseases. Treatment 19, 738, 764

The activity with which *thyroid gland* promotes the autolysis of putrefactive bacteria is sometimes illustrated in these cases. But the doses must be larger than usual, 3 grains (0.2 Gm.) every three hours, provided the heart is in good condition. In cases that are not ill enough to remain in bed, 2 grains (0.13 Gm.) every four hours suffice. The effects are improved if the sepsis is cutaneous, by giving *hypophysis sicca* ¼ grain (0.016 Gm.) with each dose of thyroid and having the patient partake freely of alkaline beverages, *Vichy and milk*, equal parts, assist in promoting renal action.

Serous Effusions 17

Shock. Treatment, 754, 764, 768, 1175, 1215, 1231, 1258; and **Heart-failure,** Treatment, 755, 758, 764, 768.

The adrenalin principle promoting energetically as catalyzer the intake of oxygen, while the posterior pituitary which contains this principle and that of the adrenal cortex, the two can be used concomitantly. *Adrenalin* 5 minims (0.3 c.c.) of the 1 to 1000 solution to the pint (500 c.c.) of saline solution is injected slowly intravenously, while 15 minims of the *liquor hypophysis* or *pituitrin* are injected intramuscularly.

Sterility. Treatment 780

This condition in stout women is often counteracted by the use of *thyroid gland* 1 grain (0.065 Gm.) *t.i.d.* *Corpus luteum* in 5-grain (0.3 Gm.) doses *t.i.d.*, has also been recommended. During pregnancy the urine should be carefully watched in such cases, as the underlying cause of sterility (unless organic) render renal complications probable, owing to imperfect catabolism of wastes due to an existing hypothyroidia. Small doses of *thyroid* ½ grain (0.03 Gm.) *t.i.d.* during pregnancy, tend to prevent this complication.

Submersion or Drowning.

The methods for the use of *adrenalin* and *liquor hypophysis* already described under *Shock* are also applicable here. When the heart fails to respond after these injections and the use of either the *Schäfer* or the *Sylvester method*, likewise fails, *pricking the heart* with a clean shawl pin introduced between the ribs, will sometimes start it. Perseverance and patience are important features of success in such cases.

Surgery.

Intramuscular injections of 8 to 15 minims (0.48 to 0.90 c.c.) of the *liquor hypophysis before* prolonged operations will tend to prevent the shock and meteorism often noted, and reduce markedly the chances of secondary hemorrhage. By enhancing the oxygen intake and tissue metabolism, it also tends to promote the efficiency of the defensive functions. When during *convalescence* the endocrin functions are defective, the process of repair is slow, while the danger of infection of the wound by endogenous bacteria, the B. coli, for instance, or exogenous organisms, is increased. In such cases small doses of *thyroid*, ½ grain (0.03 Gm.), to promote both anabolism and catabolism, and also, indirectly, phagocytosis, *strychnine* 1/60 grain (0.001 Gm.), to stimulate the adrenals and increase the intake of oxygen, and *hypophysis sicca* 1/10 grain (0.006 Gm.) to increase vascular tone, *t.i.d.*, hasten recovery noticeably. If *hemophilia* prevail, the pre-operative use of *thyroid gland* 2 grains (0.13 Gm.) and *hypophysis sicca* ¼ grain (0.016 Gm.) *t.i.d.*, or intramuscular injections of 10 minims (0.6 c.c.) of *adrenalin* in a syringeful of saline solution, given every other day, besides the *thyroid* 2 grains (0.13 Gm.), will reduce the coagulation time within safe limits, as appropriate tests will show. In *osseous diseases* the treatment indicated under BONES, DISEASES OF, this Supplement, will be found of material help.

Syphilis. General article 1795

Tetanus. General article 1429

Tetany. General article 1427

Typhoid Fever. General article, 18, 1758.

Urticaria 24

Uterine Fibroids. Treatment, 785, 786.

In cases characterized by menorrhagia and metrorrhagia, *mammary gland*, 10 to 15 grains (0.6 to 1 Gm.) four times a day, has been found efficient by several reputable authors. Briggs gives in addition, in grave cases, *extract of ergot*, 3 grains (0.2 Gm.), *extract of hydrastis* 1½ grains (0.09 Gm.) with each dose, and applies also X-ray to the ovaries every third week.

Valvular Diseases 345

Vomiting of Pregnancy. Treatment 780

In some cases this symptom is due to dilatation of the stomach owing to deficiency of adrenal hormone, the adrenals being overtaxed and unable to supply for the time being the extra needs by the process. *Liquor hypophysis* 15 minims (0.9 c.c.) injected intramuscularly, is sometimes very efficient; *corpus luteum* 10 grains (0.6 Gm.) *t.i.d.*, has also been tried, but in severe cases the oral use of remedies is often impracticable.

Yellow Atrophy of Liver 347

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